The Synthesis and Biological Activity of Nitrogen Containing Chalcones and Analogues

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Table of Contents

Chapter 2

Chapter 3

Chapter 4

ABSTRACT

Malaria is a global health problem, with an estimated 300–500 million new clinical cases and 1–2 million fatalities reported annually. Almost 90% of the incidences of malaria and deaths from the disease occur in sub-Saharan Africa. Since malaria affects mainly the poor, it is not profitable for pharmaceutical companies to develop new treatments; thus malaria is classified as a ‘neglected’ or ‘orphan disease’.

Malaria in humans, transmitted by female *Anopheles* mosquitoes, is caused by four species of *Plasmodium*, of which *P. vivax* is the most common malaria parasite, while the most severe form of malaria is caused by *P. falciparum*. These protists, the targets of antimalarial drugs, gradually develop resistance to malarial drugs. For example, quinine from the bark of the cinchona tree was the first drug against malaria. When it became obsolete in the 1940s it was replaced by chloroquine (CQ), a synthetic analogue, which is also reaching a stage of obsolescence. Many of the subsequently developed drugs are structurally related to chloroquine; thus they are or will soon be ineffective.

Artemisinin, developed from an ancient Chinese herbal medication for fever, is the latest antimalarial drug of choice. It is structurally unrelated to aminoquinoline, but resistance has already been observed in East Asia. Derivatives – including artesunate, dihydroartemisinin, artemether and arteether – are often used in combination with other antimalarial compounds to increase the half-life of a drug and delay the development of resistance to it.

Because flavonoids are not detected in human blood after oral administration (i.e. are not bioavailable), it is difficult to explain the plethora of biological activities and beneficial dietary effects reported for flavonoids. The low bioavailability of polyphenols is explained by their poor absorption in the intestines and their rapid enzymatic degradation in blood. Furthermore, according to the Lipinski rules, most commercially available drugs contain nitrogen as hydrogen bond acceptors. We thus hypothesized that the introduction of nitrogen and the removal of as many OH groups as possible from flavonoids would enhance the bioactivity and the bioavailability and, in turn, lead to new drug leads.

Since chalcones are easily synthesized from readily available commercial reagents and only a

few reports of bioactive nitrogen-containing chalcones have been published, we embarked on a project to synthesize nitrogen-containing chalcones and analogues and test their bioactivity for malaria and cancer. We used the Mannich reaction to introduce nitrogen as an aminoalkyl moiety.

Initial results with our first-generation aminoalkylated chalcones supported our hypothesis by showing moderate to good activity against malaria and cancer. Medicinal chemistry predicts that the enone moiety is responsible for both high toxicity and low bioavailability. Upon replacement of the enone moiety with a propyl moiety, *via* catalytic hydrogenation, the bioactivity of the resulting aminoalkylated diarylpropanes was increased about a hundredfold.

Consequently, we launched a programme to synthesize a wide array of aminoalkylated diarylpropane analogues, not only to enhance the bioactivity, but also to reduce the toxicity and increase the bioavailability. The Mannich reaction requires at least one aromatic OH group on one of the aromatic rings; therefore all our analogues are phenols. A total of 56 compounds were synthesized, characterized and tested for bioactivity. A smaller number was tested for toxicity and four were tested in *in vivo* mice models for bioavailability. These tests were outsourced to the University of Cape Town.

The analogues synthesized by us included compounds with different amine groups (for example piperidine, pyrrolidine, morpholine, 1-methylpiperazine, 1-ethylpiperazine, and dimethylamine), different A-ring substituents (F, Br, methyl, ethyl, butanyl, propanyl, CF_3, NH_2 etc.) including compounds with furan and thiophene A-rings, as well as other compounds, including a diarylethane and an analogue with an aminoalkyl group on both the A- and B-ring. Toxicity was seldom a constraint and most of our compounds demonstrated high selectivity indices (in excess of 7000). Most of these compounds conform to the Lipinski rules.

The first compound we tested showed bioavailability of 3%. We attributed this to first pass metabolism and attempted to protect the aromatic OH group *ortho* to the aminoalkyl group, *via* a prodrug strategy. However, this OH resisted ether and ester formation, probably due to a hydrogen bond to the aminoalkyl amine group (*via* a stable six-membered ring).

Subsequently, we established that substituents on the A-ring increase the bioavailability. The analogue with a CF_3 group on the A-ring has a bioavailability of 25%, placing it within the range of some commercially available drugs. It is not clear whether this is due to enhanced lipophilicity (*C*Log*P*) or whether a large substituent on the A-ring can protect a B-ring OH from enzymatic degradation. Work is in progress to test carbamates and other prodrugs and analogues with larger substituents on the A-ring.

Some of our compounds indicated promising activity against TK-10 (renal), UACC-62 (melanoma) and MCF-7 (breast) cancer cell lines. The best result was a TGI value of 2.11 against melanoma, which is smaller than the parthenolide TGI value of 4.47.

We believe that this thesis lays the foundations for an antimalarial drug with good bioavailability and low toxicity, which will potentially be cheap to manufacture. Since our compounds are totally unrelated to existing antimalarial compounds, resistance is not a problem, as indicated by the good activity of these compounds against chloroquine-resistant malaria strains (Dd2 and K1).

Keywords

Antimalaria, anticancer, Mannich reaction, aminoalkylated chalcones, aminoalkylated diarylpropanes, nitrogen-containing flavonoids.

OPSOMMING

Malaria is ŉ wêreldwye gesondheidsprobleem, met ŉ geraamde 300–500 miljoen nuwe kliniese gevalle en 1–2 miljoen sterftes wat jaarliks aangemeld word. Bykans 90% van alle gevalle en sterftes kom in sub-Sahara-Afrika voor. Aangesien malaria hoofsaaklik die armes raak, is dit nie winsgewend vir die farmaseutiese maatskappye om nuwe behandeling te ontwikkel nie; daarom word malaria as ŉ 'verwaarloosde' of 'wees-siekte' geklassifiseer.

Menslike malaria, wat deur die vroulike *Anopheles*-muskiet oorgedra word, word veroorsaak deur vier spesies van *Plasmodium*-spesies waarvan *P. vivax* die mees algemene malaria parasiet is, terwyl *P. falciparumen* die mees ernstige vorm van malaria veroorsaak. Hierdie protiste, die teikens van antimalariamiddels, ontwikkel geleidelik weerstand teen malarialmiddels. Kinien afkomstig uit kinabas is byvoorbeeld die eerste middel wat teen malaria gebruik is, maar het in die 1940's in onbruik geraak en is vervang met chlorokien (CQ), 'n sintetiese analoog. Hierdie middel het intussen ook grotendeels in onbruik geraak. Die meeste middels wat sedertdien ontwikkel is, is struktureel aan chlorokien verwant en is reeds of sal binnekort oneffektief wees.

Artemisinien, ontwikkel van ŉ antieke Chinese kruiemiddel teen koors, is die jongste middel teen malaria. Dit is het geen strukturele verband met aminokinolien nie, maar weerstand daarteen is reeds in Oos-Asië waargeneem. Derivate, insluitende artesunaat, dihidroartemisinien, artemeter en arte-eter, word dikwels in kombinasie met ander antimalariaverbindings aangewend ten einde die halfleeftyd van ŉ geneesmiddel te verleng en weerstandsontwikkeling te vertraag.

Aangesien flavonoïede nie in menslike bloed ná mondelinge toediening waargeneem word nie (en dus nie biobeskikbaar is nie) is dit moeilik om die oorvloed van biologiese aktiwiteite en voordelige dieetmatige uitwerkings van flavonoïede wat al gemeld is, te verduidelik. Die lae biobeskikbaarheid van polifenole word verklaar aan die hand van swak absorpsie in die dunderm, asook hulle vinnige ensimatiese afbreking in die bloed. Verder bevat die meeste kommersiële middels stikstof as waterstofbindingakseptore, volgens Lipinski se reëls. Ons hipotese was dus dat die invoer van stikstof en die verwydering van soveel as moontlik OH-groepe uit flavonoïede tot verhoogde bioaktiwiteit en biobeskikbaarheid sou lei, en

uiteindelik tot nuwe geneesmiddels.

Aangesien chalkone maklik gesintetiseer kan word van algemeen beskikbare kommersiële reagense en slegs ’n paar artikels oor bioaktiewe stikstofbevattende chalkone gepubliseer is, het ons ‘n projek onderneem om stikstofbevattende chalkone en analoë te sintetiseer en hulle bioaktiwiteit vir malaria en kanker te toets. Ons het van die Mannich-reaksie gebruik gemaak om stikstof as ’n aminoalkiel-gedeelte in te voer.

Aanvanklike resultate van ons eerste-generasie-aminoalkiel-chalkone het ons hipotese ondersteun deur gemiddelde tot goeie aktiwiteit teen malaria sowel as kanker te toon. Medisinale chemie voorspel dat die enoon-gedeelte tot hoë toksisiteit sowel as lae biobeskikbaarheid lei. Met die vervanging van die enoon-gedeelte met ’n propiel-gedeelte *via* katalitiese hidrogenering het die bioaktiwiteit van die gevolglike aminoalkiel-diarielpropane ongeveer honderdvoudig verhoog.

Ons het dus ’n program van stapel gestuur om ’n wye verskeidenheid aminoalkiel-diarielpropaan-derivate te sintetiseer ten einde die bioaktiwiteit te bevorder, toksisitiet te verlaag en biobeskikbaarheid te verbeter. Die Mannich-reaksie vereis ten minste een aromatiese OH-groep op een van die aromatiese ringe, wat al ons analoë dus fenole maak. Ons het 56 verbindings gesintetiseer, gekarakteriseer en vir bioaktiwiteit getoets. Die toksisiteit van ’n paar van hierdie verbindings is bepaal en vier van hierdie verbindings is in *in vivo*-muismodelle vir biobeskikbaarheid getoets. Hierdie toetse is na die Universiteit van Kaapstad uitgekontrakteer.

Die analoë wat deur ons gesintetiseer is, het verskillende amiengroepe bevat (bv. piperidien, pirrolidien, morfolien, 1-metielpiperasien, 1-etielpiperasien en dimetielamien), verskillende A-ring-substituente (bv. F, Br, metiel, etiel, butaan, propaan, CF_3, NH_2), insluitende verbindings met furaan en tiofeen-A-ringe, asook ander verbindings soos ’n diarieletaan en ’n verbinding met ’n aminoalkielgroep gekoppel aan die A- sowel as B-ring. Toksisiteit was selde ’n beperking en die meeste van ons verbindings het hoë selektiwiteitsindekse getoon (meer as 7000). Die meeste van hierdie verbindings het aan Lipinski se reël van vyf voldoen.

Die eerste verbinding wat ons getoets het, het ’n biobeskikbaarheid van 3% getoon. Ons het hierdie waarde aan eerste-deurgang-metabolisme toegeskryf en dus gepoog om die

aromatiese OH-groep, *orto* aan die aminoalkielgroep deur middle van ŉ voorlopergeneesmiddel-strategie te beskerm. Hierdie OH groep het egter eter- sowel as esterformasie teengewerk, waarskynlik weens ŉ waterstofbiniding aan die aminoalkielgroep (via ŉ stabiele sesledige ring). Ons het gevolglik vasgestel dat substituente op die A-ring wel biobeskikbaarheid verhoog. Die analoog met ŉ CF_3-groep op die A-ring het ŉ biobeskikbaarheid van 25% getoon, reeds in dieselfde gebied as sommige kommersiële geneesmiddels. Hierdie verhoogde waarde kan toegeskryf word aan óf verhoogde lipofilisiteit (*C*Log*P*) óf die feit dat ŉ groot substituent op die A-ring die B-ring-OH teen ensimatiese afbreking beskerm. Ons is tans besig om karbamate en ander voorlopergeneesmiddels en analoë met groter substituente op die A-ring te toets.

Sommige van ons verbindings toon belowende antiproliferatiewe aktiwiteit teen TK-10 (renale adenokarsinoom), UACC-62 (melanoom) en MCF-7 (borsadenokarsinoom) sellyne. Die beste resultaat was ŉ TGI waarde van 2.11 teen melanoom, kleiner as partenolied met ŉ TGI waarde van 4.47.

Ons is van mening dat hierdie tesis die platform skep vir die vervaardiging van ŉ goedkoop antimalariamiddel met belowende biobeskikbaarheid en lae toksisiteit. Aangesien ons verbindings geen strukturele verband met bestaande antimalariamiddels het nie, sal die ontwikkeling van weerstand nie ŉ problem wees nie, soos aangedui deur die belowende aktiwiteit teen chlorokien-weerstandige malaria-rasse (Dd2 and K1).

List of abbreviations

A	acetone
ACT	Artemisinin Combination Therapy
ADME	absorption, distribution, metabolism, excretion
AMI	Australian Army Malaria Institute
$CDCl_3$	chloroform-*d*
*C*Log*P*	octanol-water partition coefficient
CMC	Comprehensive Medicinal Chemistry
CHO	Chinese hamster ovarian
CQ	chloroquine
EtOAc	ethyl acetate
EtOH	ethanol
GI_{50}	50% growth inhibition
H	hexane
HeLa	Human Negroid cervix epitheloid adenocarcinoma
HR	High resolution
IC_{50}	Concentration at 50% inhibition
IR	Infrared spectroscopy
LC_{50}	50% lethal concentration
LC_{100}	100% lethal concentration
MDDR	Modern Drug Data Report
Me	methyl
MeOH	methanol

MMV	Medicines for Malaria Venture
MS	Mass spectrometry
MTX	methotrexate
NCI	National Cancer Institute
NMR	Nuclear magnetic resonance
P. falciparum	*Plasmodium falciparum*
PK	Pharmacokinetic
PSA	Polar Surface Area
RI	Resistance Index
RO5	“rule of five”
SI	Selectivity Index
T	toluene
TGI	Total growth inhibition
WDI	Derwent Word Drug Index
WHO	World Health Organization

1 Literature Survey

1.1 Malaria

1.1.1 The history of malaria

Mankind has been plagued by a number of infectious diseases such as measles, meningitis, tetanus and syphilis to name a few. Vaccines have been found to prevent infection of most of these diseases except one, the infamous disease known as malaria. Malaria has resisted all attempts to achieve a permanent cure or to immunize against attack. References to the unique periodic fevers associated with malaria are found throughout recorded history, beginning as early as 2700 B.C. in China.[1] Malaria was so pervasive in Rome that it was known as the "Roman Fever" and may have even contributed to the decline of the Roman Empire.[2] The term malaria originates from medieval Italian: *mala ria* meaning "bad air" and was previously known as *ague* or *marsh fever* due to its association with swamps and marshland where stagnant water was excellent breeding grounds for mosquitoes.[3] The first significant advance was made in 1880, by a French army doctor, Charles Louis Alphonse Laveran, who observed parasites inside the red blood cells of malaria sufferers. He was awarded the 1907 Nobel Prize for Physiology or Medicine for this and later discoveries.

It is estimated that 1–2 million people lose their lives to malaria and 300–500 million new clinical cases are reported annually.[4] Almost 90% of cases and deaths due to malaria occur in sub-Saharan Africa, where malaria is the leading cause of morbidity and mortality in children younger than 5 years and pregnant women, but malaria is also a serious health problem in regions of South East Asia and South America.[5] Malaria places a substantial strain on health services and costs Africa at least $12 billion in lost production annually. Malaria is Africa's most important tropical parasitic disease which is accountable for more human deaths than

[1]Cox, F. *Clinical Microbiology Reviews* **2002**, *15*, 595-612.
[2]Sallares, R.; Gomzi, S. *Ancient Biomolecules* **2001**, *3*, 195-213.
[3]Reiter, P. *Emerging Infectious Diseases* **2000**, *6*, 1-11.
[4]Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, *434*, 214.
[5]Vitoria, M.; Granich, R.; Gilks, C. F.; Gunneberg, C.; Hosseini, M.; Were, W.; Raviglione, M.; De Cock, K. M. *Am. J. Clin.Pathol.* **2009**, *131*, 844-848.

any other communicable disease, except perhaps tuberculosis and HIV-AIDS.[6] Malaria in humans, transmitted by female *Anopheles* mosquitoes, is caused by four species of *Plasmodium*, which are, *P. falciparum, P. ovale, P. vivax and P. malariae*.[7] *Plasmodium* is a genus of Apicomplexan parasites and was described in 1885 by Ettore Marchiafava and Angelo Celli.[8] There are approximately 100 known species of the genus *Plasmodium*, but only four of these cause malaria in humans. The rest infect birds, monkeys, rodents and reptiles.[9] *Plasmodium falciparum* is the most important species since it is most prevalent and the only one capable of producing fatal complications.[10,11]

The first effective treatment for malaria came from the bark of the cinchona tree, which contains quinine. The indigenous people of Peru made a tincture from cinchona to control malaria. The Jesuits noted the efficacy of this treatment and introduced it to Europe during the 1640s, however, it was not until 1820 that the active ingredient, quinine, was extracted from the bark, isolated and named.[12] In the 1940s a synthetic analogue of quinine, namely chloroquine, replaced quinine as the treatment of malaria until resistance supervened, first in Southeast Asia in the 1950s and then globally in the 1980s.[13] The current and recommended treatment for malaria, artemisinin, was discovered by Chinese scientists in the 1970s from traditionally used plant material.[14]

Diseases like malaria have led to the concept of 'neglected' or 'orphan diseases' due to the fact that they affect the poor in developing and developed countries alike. The low purchasing power of the affected populations does not spark market interest for the pharmaceutical industry[15], therefore developing countries are not only facing high-priced antimalarials, but also the increasing drug resistance of the parasite. Diseases which include African trypanosomiasis (sleeping sickness), American trypanosomiasis (Chagas disease), dengue and tuberculosis also fall into this category.

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[6]Magardie, K. *Southern Africa's biggest parasite. Mail & Guardian* **2000**, *35*, 28 July.
[7]Kaur, K.; Jain, M.; Kaur, T.; Jain, R. *Bioorg.& Med. Chem.* **2009**, *17*, 3229-3256.
[8]Chavatte, J. M.; Chiron, F.; Chabaud, A.; Landau, I. *Parasite* **2007**, *14*, 21-37.
[9]Biot, C.; Chibale, K. *Infectious Disorders – Drug Targets* **2006**, *6*, 173.
[10]Foley, M.; Tilley, L. *Pharmacol.Ther*. **1998**, *1*, 55-67.
[11]Ibezim, E. C.; Odo, U. *Afr. J. of Biotechnol.* **2008**, *7*, 349.
[12]Kaufman, T.; Rúveda, E. *AngewandteChemie* **2005**, *44*, 854-885.
[13]Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. *Malaria Journal* **2011**, *10*, 144.
[14]Hsu, E. *British Journal of Clinical Pharmacology* **2006**, *61*, 666-670.
[15]Moncayo, A.; Yanine, M.O. *Encyclopedia of Infectious Diseases, Modern Methodologies* **2007**, *669*, 603-605.

In 2007, the Bill and Melinda Gates Foundation announced the objective of eradicating malaria in conjunction with institutes such as the Roll Back Malaria partnership of the World Health Organization (WHO) and one main non-profit private partnership, Medicines for Malaria Venture (MMV).[16] Since 1996, not a single novel chemical class of antimalarials has been registered and since 2007, few reports have been provided of new anti-malarial chemotypes, thus stressing the necessity of novel drugs with novel modes of action.[17]

1.1.2 Malaria in South Africa

The worldwide distribution of malaria is indicated in Figure 1.1. The following endemicity classes can be observed: light green, hypoendemic (areas in which childhood infection prevalence is less than 10%); medium green, mesoendemic (areas with infection prevalence between 11% and 50%); dark green, hyperendemic and holoendemic (areas with an infection prevalence of 50% or more).[18]

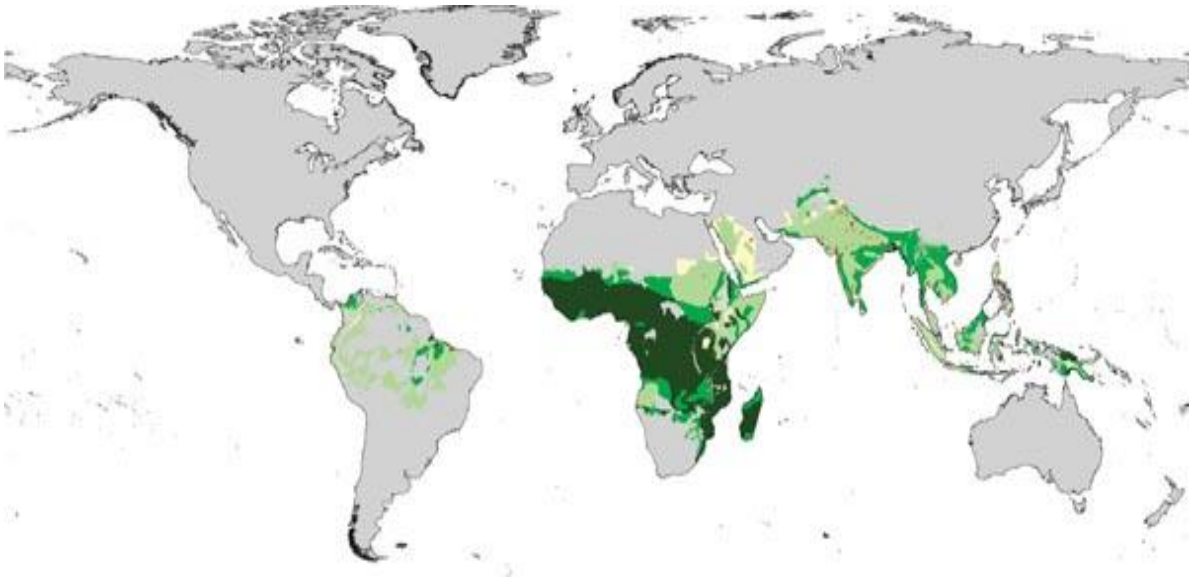


Figure 1.1: *P. falciparum* endemicity within the global limits of risk.[18]

Only approximately 10% of South Africa's estimated population of 49 million lives in malaria risk areas. Malaria is endemic in the Lowveld of Mpumalanga and in Limpopo

[16]Okie, S. *N. Engl. J. Med.* **2008**, *358*, 2425-2428.
[17]Gamo, F. J.; Sanz, L. M.; Vidal, J. *Nature* **2010**, *465*, 305-310.
[18]Murray, C. J.; Lopez, A. D. *Global Health Statistics: a Compendium of Incidence, Prevalence and Mortality Estimates for over 200 Countries* (Harvard School of Public Health, Boston/World Health Organization, Geneva), **1996**.

(including the Kruger Park and private game reserves) and on the Maputaland coast in KwaZulu Natal. Malaria is distinctly seasonal in South Africa, with the wet summer months (October to May) being the highest risk period. In the North West Province and the Northern Cape along the Molopo and Orange Rivers, including the Augrabies Falls and the Kgalagadi Transfrontier Park, malaria is only locally transmitted in exceptionally wet seasons.[19] This distribution is given in Figure 1.2.

Figure 1.2: Map of malaria areas in and around South Africa (updated 2012).[20]

1.1.3 Life cycle of the malaria parasite

The parasite requires two hosts, a female *Anopheles* mosquito and a human being. A blood meal is required for egg development in the female mosquitoes. The infected female mosquitoes withdraw blood from their victim and simultaneously inject the sporozoite form of the parasite into the human host (a). Sporozoites are then carried in the bloodstream to

[19]Tren, R.; Bate, R. *Policy analysis* **2004**, *513.*
[20]http://www.sa-venues.com/malaria-risk-areas.htm, Accessed: 19 August 2012.

liver cells, where they proliferate asexually to form thousands of merozoites each which invade red blood cells (b). An asexual cycle within the red blood cells is followed by the production of male and female gametocytes (c), which are again transmitted back to the mosquito during a subsequent blood meal (d) where they fuse and duly divide to create sporozoites (d). These then migrate to the salivary glands of the mosquito, where the cycle of infection starts again as seen in Figure 1.3.[21] Each phase represents a target, including the mosquito.

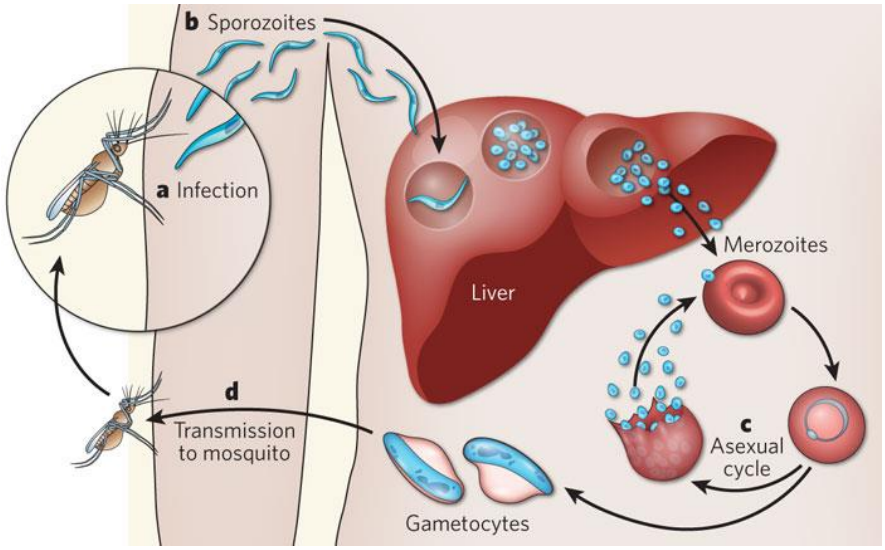


Figure 1.3: Schematic life cycle of the malaria parasite.

1.1.4 Symptoms and manifestations of malaria

The signs and symptoms of malaria typically begin 1–3 weeks following infection and may include fever, shivering, arthralgia (joint pain), vomiting, jaundice and convulsions.[22] The classic symptom of malaria is cyclical occurrence of sudden coldness followed by rigor and then fever and sweating lasting about two hours or more occurring every two days depending on the type of *Plasmodium* species causing the infection. Uncomplicated malaria (*P. vivax* and *P. ovale* infections) can be categorized into three stages as shown in Table 1.1.[23]

[21]Michalakis, Y.; Renaud, F. *Nature* **2009**, *462*, 298-300.
[22]Beare, N. A.; Taylor, T. E.; Harding, S. P.; Lewallen, S.; Molyneux, M. E. *American Journal of Tropical Medicine and Hygiene* **2006**, *75*, 790-797.
[23]Wiser, M. F. http://www.tulane.edu/~wiser/protozoology/notes/malaria/html, 2008, Accessed: 11 September 2012.

Table 1.1: The three stages of malaria paroxysm symptoms.

Stage	**Symptoms**
Cold stage	- An intense cold sensation - Severe shivering - Increased body temperature - Lasts 15-60 minutes
Hot stage	- An intense hot sensation - Increased body temperature - Severe headache, nausea, fatigue, anorexia - Lasts 2-6 hours
Sweating stage	- Severe sweating - Abating body temperatures - Exhaustion and fatigue - Lasts 4-6 hours

Severe malaria (usually caused by *P. falciparum*) leads to more complicated manifestations and may be life threatening leading to splenomegaly (enlarged spleen), hepatomeglay (enlaged liver) and hemoglobinuria with renal failure, where hemoglobin from lysed red blood cells leak into the urine.[24]

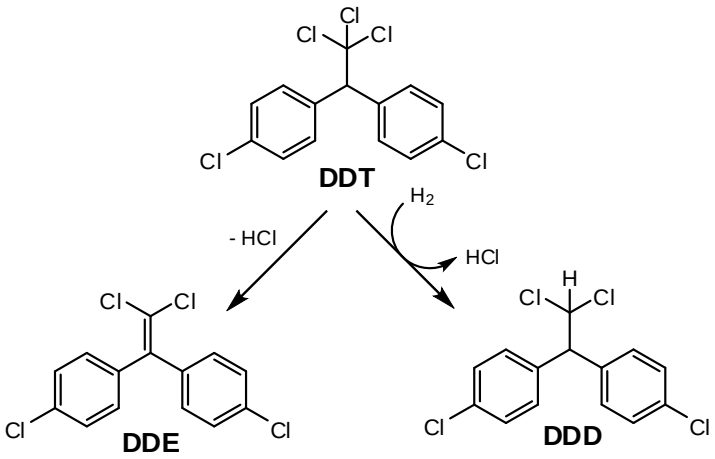
1.1.5 Malaria control measurements

Control measurements include vector control, use of bed nets, insecticides, effective therapeutic drugs and the development of potential vaccines.

DDT (dichlorodiphenyltrichloroethane) is a persistent organic pollutant which has been widely used in agriculture to control disease vectors. DDT and its metabolites (DDE - dichlorodiphenyldichloroethylene and DDD - dichlorodiphenyldichloroethane) are shown in

[24]Trampuz, A.; Jereb, A.; Muzlovic, I.; Prabhu, R. *Critical Care* **2003**, *7*, 315-323.

Scheme 1.1. These compounds have adverse effects on wildlife reproduction and bioaccumulate in predatory birds due to their hydrophobic properties.[25]



Scheme 1.1: Degradation of DDT to form DDE (HCl elimination) and DDD (reductive dechlorination).

DDT has not been used for any agricultural purposes in South Africa since 1976 but, due to the lack of suitable alternatives, DDT is currently used for indoor-malaria control in the malaria endemic areas of Kwa Zulu-Natal, Mpumalanga and Northern Province.[25]

Vector control can be accomplished by reducing vector density by implementing biological system modification to control problematic populations, destroying breeding sites or creating a barrier between the human host and the mosquito thus preventing the mosquito from feeding by means of bed-nets, repellents and protective clothing.[26] A more targeted and ecologically friendly vector control strategy involves genetic manipulation. Advances in genetic engineering technologies make it possible to introduce foreign DNA into the mosquito genome either decreasing its lifespan or making it more resistant to the malaria parasite.[27]

[25]Scott, W. E. *Malaria Control & DDT*, http://chem.unep.ch/pops/POPs_Inc/proceedings/lusaka/SCOTT.html., Accessed: 22 August 2012.
[26]Tripathi, R. P.; Mishra, R. C.; Dwivedi, N.; Tewari, N.; Verma, S. S. *Current Medicinal Chemistry* **2005**, *12*, 2643-2659.
[27]Raghavendra, K.; Barik, T. K.; Reddy, B. P.; Sharma, P.; Dash, A. P. *Parasitology Research* **2011**, *108*, 757-779.

1.1.6 Antimalarial compounds

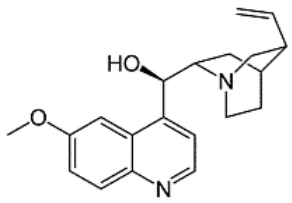
Antimalaria medications or antimalarials are designed to prevent (prophylactic) or cure malaria. These are used to treat individuals with confirmed or suspected infection, prevent infection in individuals visiting a malaria-endemic region and provide routine intermitted treatment of certain groups in endemic regions.

Chemoprophylactic therapeutic drugs inhibit certain stages in the life-cycle of the plasmodium as a preventative measure.[28] *Tissue schizonticides* for example inhibit the development of the parasites at the liver stage, while *blood schizonticides* inhibit the development on the intra-erythrocytic stage; *gametocytocides* are anti-malarial agents which prevent infection in mosquitoes by eliminating sexual forms of the parasite in hepatic circulation whereas *sporontocides* render gametocytes non-infective in the mosquito.[29]

Various chemical classes of antimalarial compounds are applied to the treatment of malaria, such as aminoquinolines (e.g. quinine, chloroquine, amodiaquine), 2,4-diaminopyrimidines (e.g. pyrimethamine), hydroxynapthoquinones (e.g. atovaquone), sulphonamides (e.g. sulfamethoxypyridazine) and antibiotics (e.g. clindamycin).[30]

1.1.7 Quinoline-based antimalarial compounds

1.1.7.1 Quinine



1

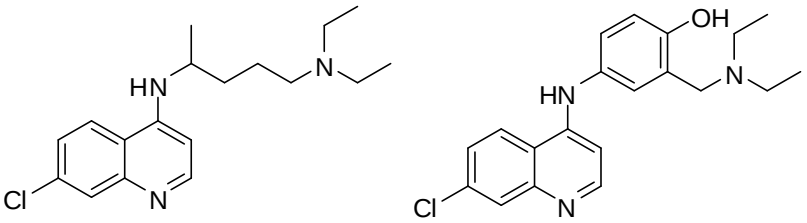
Figure 1.4: Chemical structure of quinine **1**, the first antimalarial.

[28]Ashley, E.; McGready, R.; Proux, S.; Nosten, F. *Travel Medicine and Infectious Diseases* **2006**, *4*, 159-173.
[29]Goldsmith, R. S. *Antiprotozoal drugs* (In Katzung B. G., eds. Basic and Clinical Pharmacology, 7th ed. Stamford: Appleton & Lange), **1998**, 838-861.
[30]Biot, C.; Chibale, K. *Infectious Disorders – Drug Targets* **2006**, *6*, 173.

Quinine **1** (Figure 1.4) is a white crystalline alkaloid with high sensitivity to ultraviolet light due to its highly conjugated resonance structure and occurs naturally in the bark of the *cinchona* tree. It was the first effective treatment of malaria caused by *Plasmodium falciparum*, appearing in therapeutics in the 17th century and it was listed in the London Pharmacopeia in 1677.[31] Quinine is also available in very small quantities in tonic water, which is usually enjoyed with gin. It is less effective and more toxic as a blood schizonticidal agent than chloroquine, but it is especially useful in areas with a high level of resistance to chloroquine. Quinine's toxicity, acerbity and adverse side-effects (e.g. nausea) led to the design of new synthetic alternatives in the fight against malaria.

1.1.7.2 4-Aminoquinolines

Chloroquine (CQ) **2** (Figure 1.5) is the original prototype from which most synthetic antimalarials are derived, it is also the least expensive, best tested and safest of all available antimalarials. Its effectiveness has been reduced by the emergence of drug-resistant parasitic strains. Chloroquine is a 4-aminoquinolone compound with a complicated and still unclear mechanism of action. It is believed to reach high concentrations in the vacuoles of the parasite, which raises the internal pH, due to its basic nature. It controls the conversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels of toxicity.[32] Amodiaquine **3** (Figure 1.5) is similar in structure and mode of action to chloroquine. It has been administered in areas of chloroquine resistance while some patients prefer it, due to the fact that it causes less itching than chloroquine, which is known to provoke psoriasis.[32]



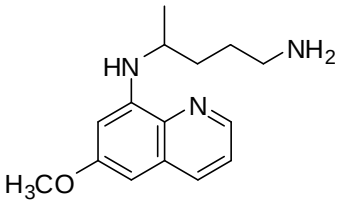
2 **3**

Figure 1.5: Stucture of chloroquine **2** and amodiaquine **3**.

[31]Wiwanitkit, V. *Malaria Research in Southeast Asia*, Nova Science Publishers, Inc., New York, **2007**, 3-11.
[32]White, N. J. *J. Clin. Invest.* **2004**, *113*, 1084-1092.

1.1.7.3 8-Aminoquinolines

The 8-aminoquinolines such as the highly active primaquine **4** (Figure 1.6) is the only effective drug against the pre-erythrocytic stages of malaria, which is not eradicated by any other drug and is highly gametocidal.[33] The first member in this class, pamaquine **5** (Figure 1.6), was developed in 1925, but it was later found to be toxic and primaquine was developed as a safer alternative.



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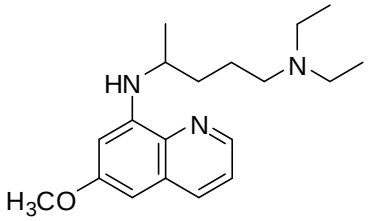
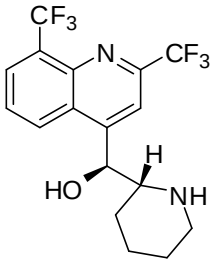


5

Figure 1.6: Chemical structures of primaquine **4** and pamaquine **5**.

1.1.7.4 4-Methanolquinolines

The 4-methanolquinoline derivatives such as mefloquine **6** (Figure 1.7) are fast acting blood schizontocides. Mefloquine is a chiral molecule with two stereogenic carbon centres.[34] It is structurally related to quinine **1** (Figure 1.4), and was introduced for routine use in 1985. Mefloquine proved useful; however, its long half-life (2–3 weeks) gave rise to resistance issues. Mental health problems such as depression, anxiety and insomnia,[32] have been related to the use of mefloquine.



6

Figure 1.7: Chemical structure of mefloquine **6**.

[33]Baird, J. K.; Fryauff, D. J.; Basri, H.; Bangs, M. J.; Subianto, B.; Wiady, I. *The American Journal of Tropical Medicine and Hygiene* **1995**, *52*, 479.
[34]Schlagenhauf, P. *Travel Med.* **1999**, *6*, 122-123.

1.1.8 Drug resistance

Drug resistance is the biggest threat to the efficacy of current antimalarials. Drug resistance or antimicrobial resistance occurs when the parasite changes in ways that render the medication used to cure the disease they cause, ineffective. Since 1945, chloroquine has been effective in the fight against malaria; however, 12 years later, the first case of chloroquine resistant *P. falciparum* malaria was reported.[35] These dates of introduction and resistance are shown in Table 1.2.

Table 1.2: Antimalarial drug resistance of a few known drugs.[35]

Antimalarial drug	Introduced	First reported resistance	Difference (years)
Quinine	1632	1910	278
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Mefloquine	1977	1982	5
Atovaquone	1996	1996	0

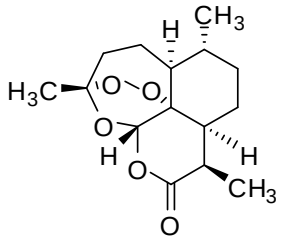
Many factors contribute to the development and spread of drug resistance. These factors include human host factors, parasite characteristics, drug-use patterns and vector and environmental factors which may influence the proliferation of resistant parasites.[36]

1.1.9 Artemisinin and analogues

Artemisinin **7** (Figure 1.8) occurs in a Chinese herb that has been used to treat fevers for over 1000 years, thus predating the use of quinine **1** (Figure 1.4) in the western world. It has been isolated from the plant *Artemisia annua* (sweet wormwood or qinghao). It is a sesquiterpene lactone, with its antimalarial power believed to be in its rare peroxide bridge linkage.[37] Artemisinin has excellent antimalarial activity against chloroquine resistant *P. falciparum*,[38]

[35]Wongsrichanalai, C.; Pickard, A. L.; Wernsdorfer, W. H.; Meshnick, S. R.*The lancet infectious diseases* **2002**, *2*, 209-218.
[36]Wernsdorfer, W. H.; Payne, D. *Pharmacol.Ther.* **1991**, *50*, 95-121.
[37]Meshnick, S. R. *International Journal of Parasitology* **2002**, *32*, 1655-1660.
[38]Luo, X-D.; Shen, C-C. *Med. Res. Rev.* **1987**, *7*, 29.

as well as its *in vitro* activity against *Pneumocystis carinii*[39] and *T. gondii*.[40] It is not suitable as a prophylactic due to its short elimination half-life of 2–5 hours.



7

Figure 1.8: Chemical structure of artemisinin **7**.

According to Jung, the unique structure bearing an endoperoxide could generate active oxygen radicals *via* hemolytic cleavage of the weak oxygen bond, which may cause damage to cellular structures of the active cancer cells.[40]

Dihydroartemisinin **8** (Figure 1.9) is an active metabolite to which artemesinin can be reduced, and from which many derivatives have been synthesized such as artemether **9**, arteether **10** and sodium artesunate **11** (Figure 1.9) which is currently in use.

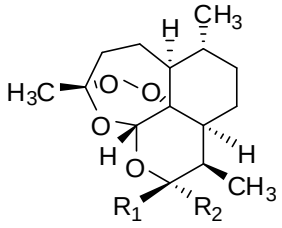


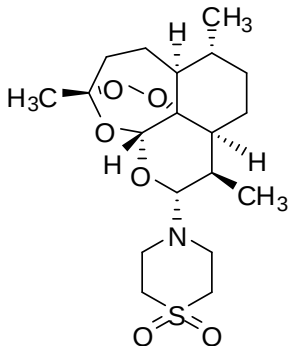
Figure 1.9: Chemical structure of artemisinin derivatives such as dihydroartemisinin **8** (R_1 = OH, R_2 = H), artemether **9** (R_1 = OMe, R_2 = H), arteether **10** (R_1 = OEt, R_2 = H) and sodium artesunate **11** (R_1 = $OCO(CH_2)_2CO_2Na$, R_2 = H).

Slow and incomplete absorption of artemisinin, dihydroartemisinin, artemether and arteether due to poor water-solubility, leads to sodium artesunate being better absorped due to its

[39]Merali, S.; Meshnick, S. R. *Antimicro. Agents Chemother.* **1991**, *35*, 1225.
[40]Jung, M. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 1091-1094.

hydrophilic nature, although instability issues and short plasma half-life limits its usefulness.[41,42]

More recent research led to a new semi-synthetic compound which can be synthesized from dihydroartemisinin in a one-step process, namely artemisone **12** (Figure 1.10).[43] This artemisinin derivative shows increased antimalarial activity, improved stability and bioavailability, with a healing effect at dose levels almost half of those of artesunate. Studies have shown increased efficacy of artemisone **12** against multi-drug resistant *P. falciparum* which may lead to new artemisinin combination therapies in the future.[44]



12

Figure 1.10: Chemical structure of artemisone **12**.

1.1.10 Artemisinin Combination Therapy (ACT)

The short half-life of artemisinin derivatives is a major limitation resulting in rapid elimination. Frequent administration is needed which leads to noncompliance and recrudescence. Patients usually stop the courses once they feel better or they want to save the medicine for another time. Thus, artemisinin treatments are only effective in combination with longer half-life drugs which are not effective if taken on their own. These issues gave

[41]Ilett, K. F.; Batty, K. T. *Artemisinin and its derivatives*, (In Yu, V. L.; Edwards, G.; McKinnon, P. S. & Peloquin, C. eds. Antimicrobial Therapy and Vaccines. Vol II. Antimicrobial drugs. London: ESun Technologies LLC.), **2004**, 957-978.
[42]Lin, A. J.; Lee, M.; Klayman, D. L. *J. of Med. Chem.* **1989**, *32*, 1249-1252.
[43] Haynes, R. K.; Ho, W. Y.; Chan, H. W.; Fugmann, B.; Stetter, J.; Croft, S. L.; Vivas, L.; Peters, W.; Robinson, B. L. *Angewandte Chemie* **2004**, *116*, 1405-1409.
[44]Vivas, L.; Rattray, L.; Stewart, L. B.; Robinson, B. L.; Fugmann, B.; Haynes, R. K.; Peters, W.; Croft, S. L. *J. Antimicrob. Chemother.* **2007**, *59*, 658-665.

rise to artemisinin combination therapy (ACT) and this became the new weapon in the fight against drug resistance and also highlights the serious need for a single-dose cure for malaria.

Studies done by the Australian Army Malaria Institute (AMI) reported that the addition of mefloquine **6** (Figure 1.7) to artemisone **12** (Figure 1.10) might cure infected monkeys, but the long presence of mefloquine **6** in the body runs the risk of developing resistance in reinfected patients.[45] This led to the work of Obaldia III and co-workers in 2009 who demonstrated the combination of artemisone **12** with amodiaquine **3** (Figure 1.5) as a possible curative 3-day treatment in monkeys. This treatment still has to be proven effective in humans.[46]

The ACTs currently recommended by WHO are artesunate/amodiaquine, artemether/lumefantrine and artesunate/mefloquine.[47]

1.1.11 New malaria drugs in development

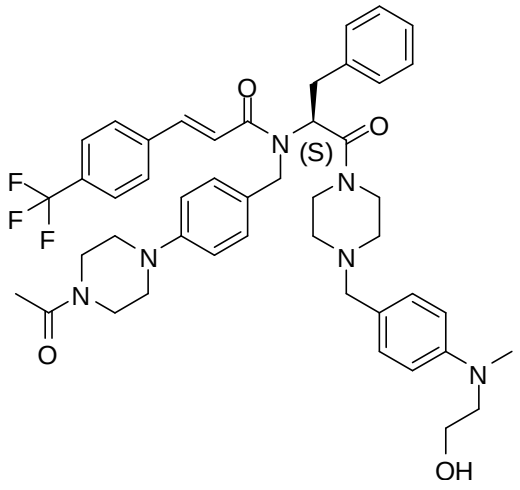
In 2012, Brunner and co-workers[48] described the *in vitro* and *in vivo* properties of a new chemotype known as ACT-213615 (Figure 1.11). The mode of action from ACT-213615-treated *in vitro* cultures was distinct from that of other antimalarials, although the molecular target of this new compound is yet to be unveiled. Further research and development of this compound with its novel mode of action is still continuing.

[45]Haynes, R. K.; Fugmann, B.; Stetter, J.; Rieckmann, K..; Heilmann, H. D.; Chan, H. W.; Cheung, M. K.; Lam, W. L.; Wong, H. N.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Peters, W.; Robinson, B. L.; Edstein, M. D.; Kotecka, B.; Kyle, D. E.; Beckermann, B.; Gerisch, M.; Radtke, M.; Schmuck, G.; Steinke, W.; Wollborn, U.; Schmeer, K.; Romer, A. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2082-2088.

[46]Obaldia III, N.; Kotecka, B. M.; Edstein, M. D.; Haynes, R.; Fugmann, B.; Kyle, D. E.; Rieckmann, K. H. *Antimicrob. Agents Chemother.* **2009**, *53*, 3592.

[47]World Health Organization 2011, "World Malaria Report 2011".

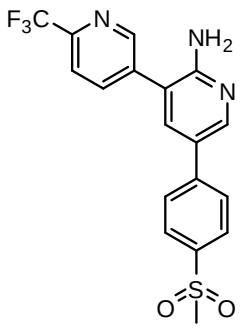
[48]Brunner, R.; Aissaoui, H.; Boss, C.; Bozdech, Z.; Brun, R.; Corminboeuf, O.; Delahaye, S.; Fischli, C.; Heidmann, B.; Kaiser, M.; Kamber, J.; Meyer, S.; Papastogiannidis, P.; Siegrist, R.; Voss, T.; Welford, R.; Wittlin, S.; Binkert, C. *Journal of Infectious Diseases* **2012**, *206*, 735-743.



13

Figure 1.11: Structure of the active enantiomer of ACT-213615 **13**.

In 2012, Prof. Kelly Chibale and his team made headlines with a potential single, oral dose cure against malaria. This compound, which forms part of a novel class of orally active antimalarial 3,5-diaryl-2-aminopyridines (Figure 1.12), completely cured *Plasmodium berghei*-infected mice with a single oral dose of 30 mg/kg. CQ **2**, mefloquine **6**, and the artemisinins do not achieve a single oral dose cure in this *P. berghei* model. Good bioavailability (51% at 20 mg/kg), a reasonable half-life ($t_{½}$ ~ 7–8 h) and the fact that it is superior to CQ in the K1 strain makes this compound a very good candidate for further investigation.[49] It is believed that clinical testing will proceed in the near future.



14

Figure 1.12: Structure of the promising 3,5-diaryl-2-aminopyridine derivative **14**.

[49]Younis, Y.; Douelle, F.; Feng, T-S.; Cabrera, D. G.; Le Manach, C.; Nchinda, A. T.; Duffy, S.; White, K. L.; Shackleford, D. M.; Morizzi, J.; Mannila, J.; Katneni, K.; Bhamidipati, R.; Zabiulla, K. M.; Joseph, J. T.; Bashyam, S.; Waterson, D.; Witty, M. J.; Hardick, D.; Wittlin, S.; Avery, V.; Charman, S. A.; Chibale, K. *J. Med. Chem.* **2012**, *55*, 3479-3487.

1.1.12 Malaria vaccines

The need for a malaria vaccine is evident when looking at the problems with pharmaceutical treatments such as cost, negative side-effects, development of resistance and drug compliance. Such a vaccine should ideally control both the malaria transmission and the intensity of the infection.

Some resistance against malaria seems to be present in populations living in malaria infected areas. This may however be genetic (e.g. sickle cell anemia). Progress and breakthroughs have often been claimed. But so far only one compound has made it into phase III trials namely RTS,S.[50] This is due to many challenges such as financial strain, but the most challenging is to develop a vaccine which is effective against all life cycle stages of the parasite.[51] The lack of understanding of the protective immune mechanisms and target antigens has made it difficult to identify candidates for further development.

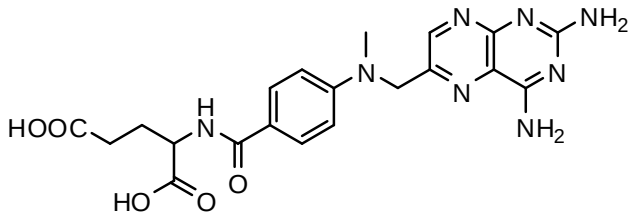
1.1.13 Malaria and cancer – is there a link?

Drug repositioning involves the use of existing drugs against alternative diseases. This approach is attractive as bioavailability and toxicity issues have been solved during registration for the existing use. Some antimalarials are now used for other treatments such as chloroquine which is used for the management of rheumatoid arthritis[52] and quinine to treat muscle cramps.[53] Sulfur-based antibacterial drugs were the first drugs to be repositioned for the treatment of malaria. The successful treatment of bacterial infections with prontosil – a prodrug which is converted to sulfanilamide – has led to the synthesis of many sulfone derivatives to treat other infectious diseases such as malaria.[54]

Since bacteria, malaria parasites and cancer cells are rapidly dividing cells, it seems reasonable to postulate that some of the critical cell division pathways can be inhibited by the same compounds. This concept is proved by methotrexate (MTX) (Figure 1.13), an

[50]Malaria Vaccine Initiative.http://www.malariavaccine.org/RTSSPhase3, Accessed 23 March 2013.
[51]Al-Hussaieny, N. H. *Parasitologists United Journal* **2010**, *3*, 1-8.
[52]Sibilia, J.; Pasquali, J. L. *Presse Med.* **2008**, *37*, 444-459.
[53]Miller, T. M.; Layzer, R. B. *Muscle Nerve* **2005**, *32*, 431-442.
[54]Nzila, A.; Ma, Z.; Chibale, K. *Future Med. Chem.* **2011**, *3(11)*, 1413-1426.

anticancer drug that blocks malaria parasite growth *in vivo*.[55,56]



15

Figure 1.13: Chemical structure of methotrexate **15**.

Artemisinin analogues have shown anticancer properties, through their ability to reduce cell numbers in solid tumours *in vitro*[57] and in *ex vivo*[58] animal models. A recent phase II study in patients with lung cancer reported that artemisinin combinations can possibly extend short-term survival as well as time-to-progression rates.[59]

There thus seem to be some correlation between drugs that are bioactive against cancer and malaria cells.

1.2 Biologically active flavonoids and the synthesis of nitrogen containing analogues

1.2.1 Flavonoids

Flavonoids are polyhydroxy secondary metabolites that are ubiquitous in plants and thus an important constituent of the human and animal diet. They can be described as 2-arylchroman compounds. Their biosynthetic origin from condensation of a cinnamoyl-CoA starter unit with three molecules of malonyl-CoA explains their C_6-C_3-C_6 formula and polyhydroxy nature. Despite this deceptively simple biosynthetic origin and C_6-C_3-C_6 formula, a large

[55]Sheehy, T. W.; Dempsey, H. *JAMA* **1970**, *214*, 109-114.
[56]Wildbolz, A. *Ther. Umsch.***1973**, *30*, 218-222.
[57]Chen, H. H.; Zhou, H. J.; Fang, X. *Pharmacol. Res.* **2003**, *48*, 231-236.
[58]Chen, H.; Sun, B.; Pan, S.; Jiang, H.; Sun, X. *Anticancer Drugs* **2009**, *20*, 131-140.
[59]Zhang, Z. Y.; Yu, S. Q.; Miao, L. Y.; Huang, X. Y.; Zhang, X. P.; Zhu, Y. P.; Xia, X. H.; Li, D. Q. *Zhong.Xi.Yi.Jie.He.Xue.Bao.* **2008**, *6*, 134-138.

number of flavonoids have been isolated, some with complex structures. Figure 1.14 gives a few examples from the different classes of flavonoids.

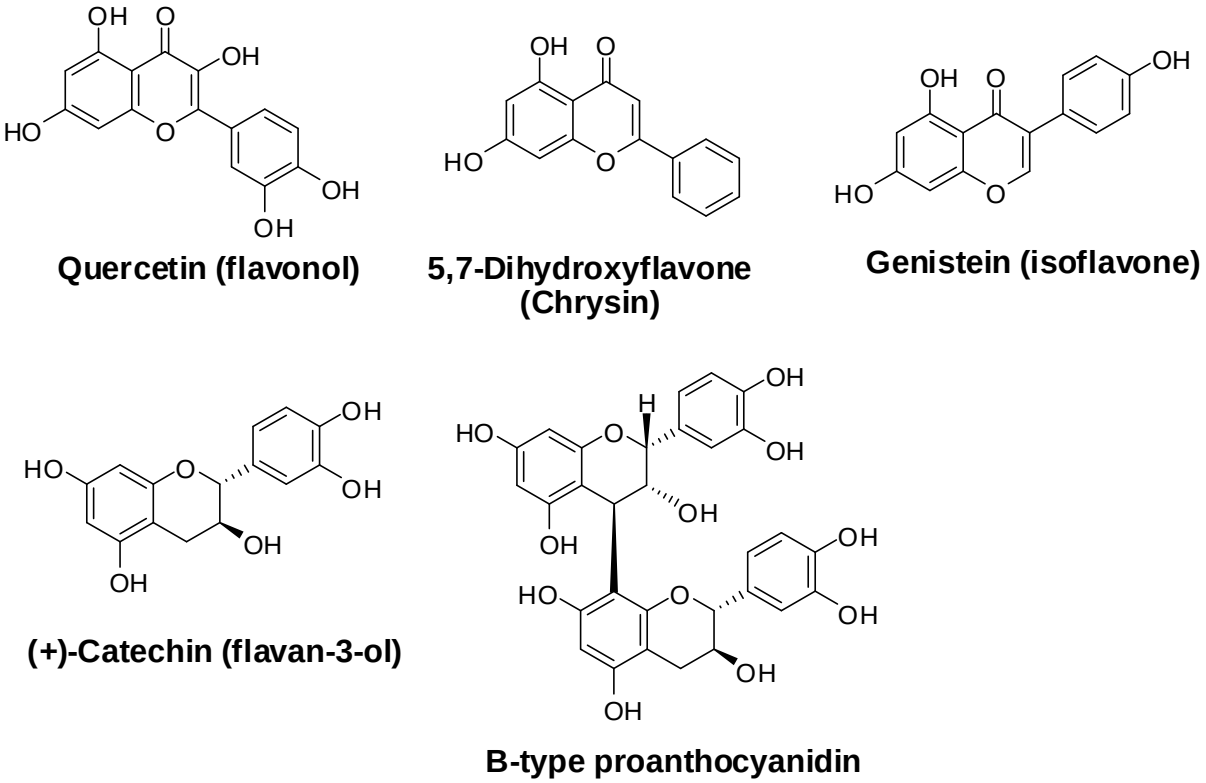


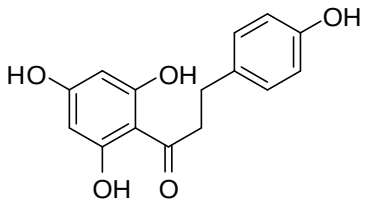
Figure 1.14: Examples from the different classes of flavonoids.

A plethora of *in vitro* biological activities have been reported for flavonoids including antimicrobial,[60] anti-inflammatory[61] and anticancer[62] properties. Many beneficial health effects such as longevity have been attributed to regular consumption of flavonoid rich foods. The bioavailability of flavonoids is controversial. Polyphenols are metabolized by liver enzymes, leading to reduced bioavailability and to high levels of conjugates in the plasma and urine.[63] Polar compounds are also not well absorbed by the digestive system. It thus remains difficult to reconcile their poor or zero bioavailability with their putative health effects and progress in their pharmaceutical use has been limited.

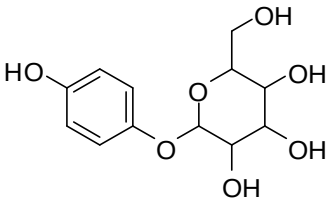
[60]Cushnie, T. P. T.; Lamb, A. J. *International Journal of Antimicrobial Agents* **2011**, *38(2)*, 99-107.
[61]Yamamoto, Y.; Gaynor, R. B. *Journal of Clinical Investigation* **2001**, *107*, 135-142.
[62]De Sousa, R. R.; Queiroz, K. C.; Souza, A. C.; Gurgueira, S. A.; Augusto, A. C.; Miranda, M. A.; Peppelenbosch, M. P.; Ferreira, C. V.; Aoyama, H. *J. Enzyme Inhib. Med. Chem.* **2007**, *22(4)*, 439-444.
[63]Walle, T. *Free Radical Biol. Med.* **2004**, *36*, 829-837.

1.2.2 Chalcones

Chalcones (1,3-diaryl-2-propen-1-one) are intermediates in the biosynthesis of flavonoids from cinnamoyl-CoA and malonyl-CoA.[64] They are open-chain flavonoids with the two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system. Chalcones are important in their own right and many chalcones have been isolated and demonstrated to have *in vitro* bioactivities such as analgesic, anti-inflammatory, antibacterial, antimycotic, antiviral, anticancerous and antiprotozoal properties.[65,66,67,68,69] Recent studies have shown that chalcones limit cancer cell proliferation, are potent agents *in vivo* against skin carcinogenesis[70] and show effects on tumor angiogenesis.[71] Figure 1.15 gives the structures of phloretin, a chalcone derivative present in apples and arbutin, present in strawberries and wheat.[72]



Phloretin



Arbutin

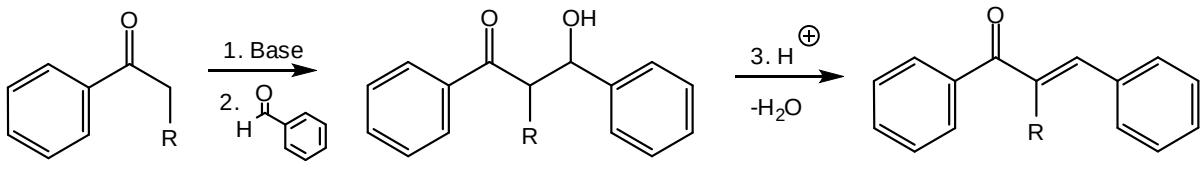
Figure 1.15: Chemical structures of phloretin and arbutin.

1.2.3 Synthesis of chalcones

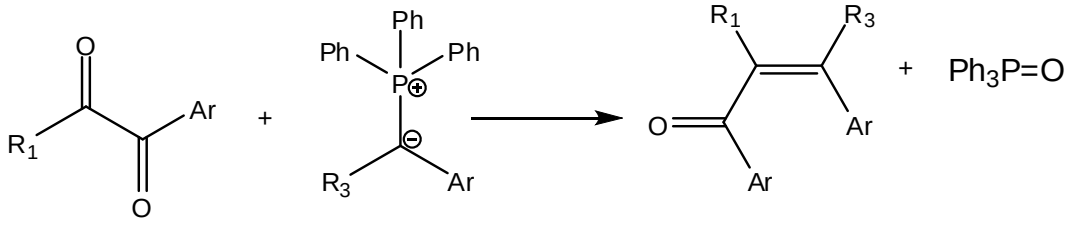
Chalcones are mainly synthesized by the classical Claisen-Schmidt condensation with aqueous alkaline bases (Scheme 1.2). They are also synthesized *via* the Wittig reaction

[64]Reddy, M. V. B.; Su, C-R.; Chiou, W-F.; Liu, Y-N.; Chen, R. Y-H.; Bastow, K. F.; Lee, K-H.; Wu, T-S. *Bioorg.& Med. Chem.* **2008**, *16*, 7358-7370.
[65]Dimmock, J. R.; Elias, D. W.; Beazely, M. A.; Kandepu, N. M. *Curr. Med. Chem.* **1999**, *6*, 1125-1149.
[66]Go, M. L.; Wu, X.; Liu, X. L. *Curr. Med. Chem.* **2005**, *12*, 483-499.
[67]Ni, L.; Meng, C. Q.; Sikorski, J. A. *Expert Opin.Ther. Patents* **2004**, *14*, 1669-1691.
[68]Yit, C. C.; Das, N. P. *Cancer Lett.* **1994**, *82*, 65-72.
[69]Ramanathan, R.; Tan, C. H.; Das, N. P. *Cancer Lett.* **1992**, *62*, 217-224.
[70]Statomi, Y. *Int. J. Cancer* **1993**, *55*, 506-514.
[71]Ivanova, Y.; Momekov, G.; Petrov, O.; Karaivanova, M.; Kalcheva, V. *European Journal of Med. Chem.* **2007**, *42*, 1382-1387.
[72]Echeverria, C.; Santibañez, J. F.; Donoso-Tauda, O.; Escobar, C. A.; Ramirez-Tagle, R. *Int. J. Mol. Sci.* **2009**, *10*, 221-231.

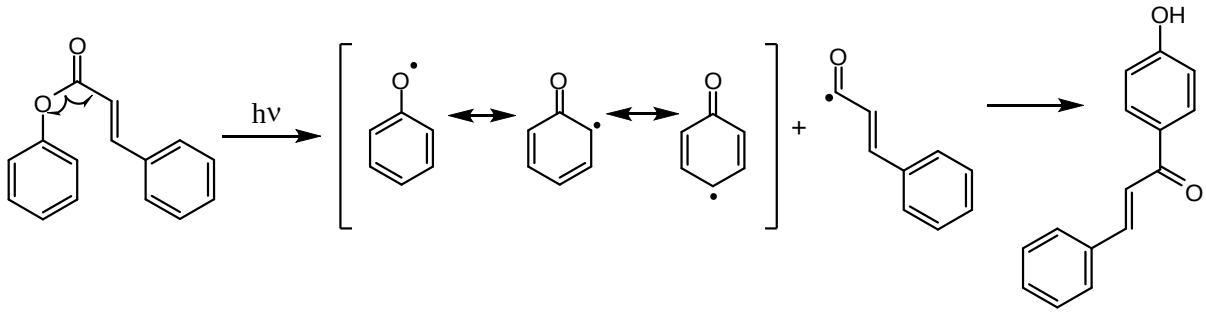
(Scheme 1.3)[73] or by Photo Fries rearrangement (Scheme 1.4) of phenyl cinnamates[74].



Scheme 1.2: Reaction scheme of Claisen-Schmidt condensation.



Scheme 1.3: Reaction scheme of the Wittig reaction.



Scheme 1.4: Reaction scheme of Photo Fries rearrangement.

1.2.4 Biologically active chalcones

The common α,β-unsaturated ketone system is believed to be responsible for the broad spectrum of biological activities observed. The elimination of this structural moiety leads to the absence of bioactivity.[75]

[73]Xu, C.; Chen, G.; Huang, X. *Prep. Proced. Int.* **1995**, *27*, 559.
[74]Dhar, D. N. *The Chemistry of chalcones and related compounds*, John Wiley & Sons, New York, 1981.
[75]Sahu, N. K.; Balbhadra, S. S.; Choudhary, J.; Kohli, D. V. *Curr. Med. Chem.* **2012**, *19*, 209-225.

The pharmacological activities combined with the ease of synthetic reproduction and derivatization of the core structure has sparked great interest for the discovery of proposed lead compounds.[65]

Chalcones are characterized by a low tendency to interact with DNA, unlike other conventional cytotoxic agents, which to a great extent minimizes the risk of mutagenicity and carcinogenicity common in most chemotherapeutics. This advantage has led to intensive research with both natural and synthetic chalcones focusing on the development of novel, patient-friendly cytotoxic agents.[76] Antioxidant flavonoids (including chalcones) owe their cytotoxicity to their pro-oxidant effects.[77] The complex pharmacodynamics and the diverse structure of chalcones means that there are no structure activity rules affording optimal cytotoxicity, although aryl moieties substitution and the abundance of the enone system seem to be crucial for the cytotoxic activity of chalcones.[78,79]

Bioavailability of chalcones from food sources is limited, but the bioavailability of synthetic chalcones has been widely reported.[80]

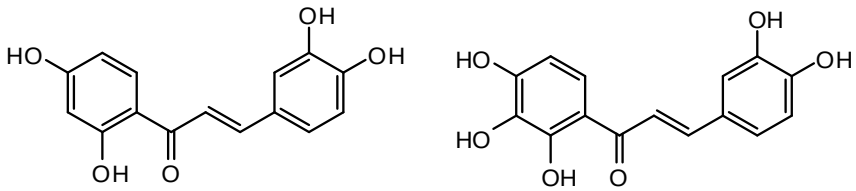
Due to the rapid first-pass metabolism and their polyphenolic nature, it is well known that phenols have low bioavailability. Furthermore, natural occurring chalcones do not conform to the Lipinski rules and are usually insoluble in water. However, several pure chalcones isolated from plants have shown very promising bioactivity and are currently being used in clinical trials as anticancer compounds as well compounds against cardiovascular disorders.

A few of the most significant naturally occurring chalcones and their biological activities are outlined in the following few paragraphs.

[76]Douglas Kinghorn, A.; Farnsworth, N. R.; DoelSoejarto, D.; Cordell, G. A.; Pezzuto, J. M.; Udeani, G. O.; Wani, M. C.; Wall, M. E.; Navarro, H. A.; Kramer, R. A.; Menendez, A. T.; Fairchild, C. R.; Lane, K. E.; Forenza, S.; Vyas, D. M.; Lam, K. S.; Shu, Y-Z. *Pure Appl. Chem.* **1999**, *71*, 1611-1618.
[77]Rozmer, Z.; Berki, T.; Perjési, P. *Toxicol. Vitro* **2006**, *20*, 1354-1362.
[78]Lawrence, N. J.; McGown, A. T. *Curr. Pharm. Des.* **2005**, *11*, 1679-1693.
[79]Hadfield, J. A.; Ducki, S.; Hirst, N.; McGown, A. T. *Prog. Cell Cycle Res.* **2003**, *5*, 309-325.
[80]Hijova, E. *Bratisl. Lek. Listy.* **2006**, *107(3)*, 80-84.

1.2.4.1 Antioxidant activity

Almost all flavonoids have been associated with antioxidant activity. Butein, for example (Figure 1.16), a chalcone found in *Toxicodendron vernicifluum* also known as the Chinese lacquer tree and okanin (Figure 1.16), a chalcone from the plant *Bidenspilosa* showed effective antioxidant properties.[81]



16 **17**

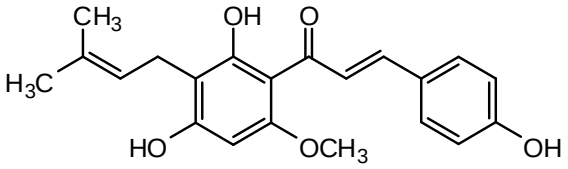
Figure 1.16: Chemical structures of butein **16** and okanin **17**.

The substitution on the two aryl rings and their substitution patterns greatly influence the antioxidant properties of chalcones. One of the main groups which greatly improve the antioxidant activity of chalcones is the hydroxyl substituent due to its ease of conversion to phenoxy radicals *via* the hydrogen atom transfer mechanism.[82]

1.2.4.2 Anticancer activity

Antiproliferative and tumor-reducing activities of chalcones have sparked new interest in identifying naturally occurring chalcones as potentially useful compounds in cancer chemotherapy.[83] Xanthohumol **18**, a prenylatedchalcone from hops and beer, has been identified as a potential chemopreventive agent during prostate hyperplasia and prostate carcinogenesis.[84]

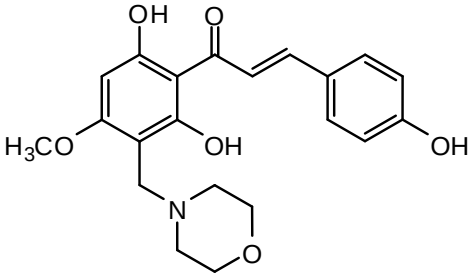
[81]Dziedzic, S. Z.; Hudson, B. J. F. *Food Chem.* **1983**, *12*, 205-212.
[82]Rezk, B. M.; Haenen, G. R. M. M.; Van der Vijgh, W. F. F.; Bast, A. *Biochim. Biophys. Res. Commun.* **2002**, *295*, 9.
[83]Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N.E.; Huang, P.; Khana, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491-3495.
[84]Mendes, V.; Monteiro, R.R.; Pestana, D.; Teixeira, D.; Calhau, C. A. O.; Azevedo, I. *J. Agric. Food Chem.* **2008**, *56*, 11631-11637.



18

Figure 1.17: Chemical structure of xanthohumol **18**.

Reddy and co-workers synthesized Mannich bases of heterocyclic chalcones of which (*E*)-1-(2,6-dihydroxy-4-methoxy-3-(morpholinomethyl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one **19** (Figure 1.18) was the most active compound in the whole series.[64]

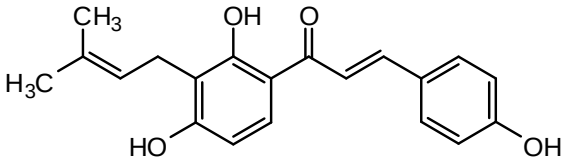


19

Figure 1.18: Chemical structure of (*E*)-1-(2,6-dihydroxy-4-methoxy-3-(morpholinomethyl)-phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one **19**.

Isobavachalcone **20** (Figure 1.19) isolated from *Angelica keiskei*, was investigated by Nishimura and co-workers and they reported cytotoxicity against neuroblastoma cell lines IMR-32 and NB-39 with no effect on healthy cells, even at elevated concentration exposure, which suggests that isobavachalcone induces apoptosis in neuroblastoma *via* the mitochondrial pathway.[85]

[85]Nishimura, R.; Tabata, K.; Arakawa, M.; Ito, Y.; Kimura, Y.; Akishisa, T.; Nagai, H.; Sakuma, A.; Kohno, H.; Suzuki, T. *Biol. Pharm. Bull.* **2007**, *30*, 1878-1883.

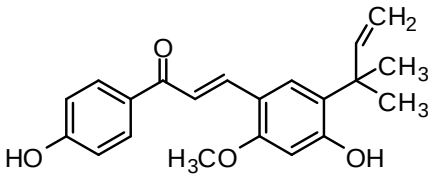


20

Figure 1.19: Chemical structure of isobavachalcone **20**.

1.2.4.3 Antimalarial activity

Licochalcone A **21** (Figure 1.20) was isolated from Chinese liquorice roots and was the first chalcone to be reported for its antimalarial activity.



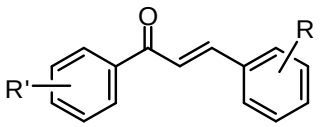
21

Figure 1.20: Chemical structure of licochalcone A **21**.

A series of hydroxylated and alkoxylated chalcones were synthesized by Liu et al.[86] and evaluated for *in vitro* antimalarial bioactivity against *P. falciparum*. The antimalarial bioactivity of these compounds is given in Table 1.3.

[86]Liu, M.; Wilairat, P.; Go, M. L. *J. Med. Chem.* **2001**, *44*, 4443-4452.

Table 1.3: Antimalarial bioactivity of substituted alkoxychalcones



Compound	R'	R	IC_{50} (μM)
22	2',3',4'-trimethoxy	4-trifluoromethyl	3.0
23	2',3',4'-trimethoxy	3-quinolinyl	2.0
24	2',4'-dimethoxy	2,4-dimethoxy	2.1
25	2',4'-dimethoxy	4-ethyl	2.4
26	2',4'-dimethoxy	3-quinolinyl	2.2
27	4'-methoxy	4-hydroxy	7.0
Chloroquine	-	-	0.265

Table 1.3 shows that trimethoxy, dimethoxy and methoxy showed good IC_{50} values. Alkoxylated chalcones showed better bioactivity compared to the corresponding hydroxylated chalcones; therefore the hydrophobicity and size of substituents play an important role in bioactivity.

Bandgar and co-workers[87] reported the synthesis and biological activity of methoxychalcones as anticancer and antioxidant agents. They analysed their compounds in terms of several theoretical parameters such as *C*Log*P*, polar surface area (PSA), molecular weight, hydrogen bond acceptors (HBA) and also to the Lipinski rule of five[88] (page 32), due to their consideration of oral delivery. These compounds were found to be non-toxic and further development is underway. Bandgar only made modifications on the B-ring such as Br, Cl, F and NO_2 in the 4-position; the A-ring only differed in the number and positions of the methoxy groups.

[87]Bandgar, B. P.; Gawande, S. S.; Bodade, R. G.; Totre, J. V.; Khobragade, C. N. *Bioorg. Med. Chem.* **2010**, *18*, 1364-1370.
[88]Lipinski, C. A. *Drug Discovery Today* **2004**, *1*, 337.

The substitution of hydrogen by fluorine has paved the way to potent biologically active compounds without many stereochemical changes due to its small size.[89] This substitution is however known to regulate overall stability and reactivity of the compounds due to the C-F bond's resistance toward metabolic transformation and electronegativity differences, which give rise to changes in acidity.[90] A few reports have mentioned the increased biological activity of fluorinated chromones[91] and fluorinated methoxychalcones[92] compared to the non-fluorinated analogues. Replacement of a C-H or C-OH bond by a C-F bond in biologically active compounds alters the physicochemical aspects of the compound, without the introduction of major steric changes,[89] and therefore useful alterations in biological activities result from these substitutions.

Padhye and co-workers[93] only substituted the B-ring with hydroxyl/fluoro groups since there is evidence suggesting that these modifications on the A-ring can modulate antioxidant systems leading to mitochondrial oxidative stress which can lead to apoptosis.[94] Their work focused on the evaluation of these compounds's radical scavenging potential and anti-proliferative activities against human pancreatic and breast cancer cells and their results suggest that chalcones fluorinated in the B-ring show better anti-proliferative activities than their hydroxylated counterparts.

A study reported that 4'-aminochalcones and related Schiff bases and maleamic acids exert cytotoxic activity at low concentrations against P388 and L1210 murine leukemia cell lines.[95] According to these findings, Ivanova *et al*. prepared a series of 12 Mannich bases, derived from a chalcone with a condensed oxazole ring and performed *in vitro* testing on their cytotoxic effects.[96] Ivanova's synthesized compounds were evaluated for cytotoxicity in the

[89]Smart, B. E. Characteristics of C-F Systems. In *Organofluorine Chemistry: Principles and Commercial Applications;* Banks, R. E.; Smart, B. E.; Tatlow, J. C. Eds.; Plenum Press: New York, 1994, 57.
[90]Kirk, K. L. Fluorine Substitution as Modulator of Biological Processes. In *Biomedical Chemistry: Applying Chemical Priciples to the Understanding and Treatment of Disease*; Torrence, P. F. Ed.; John Wiley & Sons: New York, 2000, 247.
[91]Ishar, M. P.; Singh, G.; Singh, S.; Sreenivasan, K. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1366.
[92]Nakamura, C.; Kawasaki, N.; Miyataka, H.; Jayachandran, E.; Kim, I. H.; Kirk, K. L.; Taguchi, T.; Hori, H.; Satoh, T. *Bioorg. Med. Chem.* **2002**, *10*, 699.
[93]Padhye, S.; Ahmad, A.; Oswal, A.; Dandawate, P.; Rub, R. A.; Deshpande, J.; Swamy, K. V.; Sarkar, F. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5818-5821.
[94]Guzy, J.; Vaskova-Kubalkova, J.; Rozmer, Z.; Fodor, K.; Marekova, M.; Poskrobova, M.; Perjési, P. *FEBS Lett.* **2010**, *584*, 567.
[95]Dimmock, J. R.; Jha, A.; Zello, G. A.; Allen, T. M.; Santos, C. L.; Balzarini, J.; De Clercq, E.; Manavathu, E. K.; Stables, J. P. *Pharmazie* **2003**, *58*, 227-232.
[96]Ivanova, Y.; Momekov, G.; Petrov, O.; Karaivanova, M.; Kalcheva, V. *European Journal of Medicinal Chemistry* **2007**, *42*, 1382-1387.

human pre-B-cell leukemia cell line BV-173 using the MTT-dye reduction assay. Although they have yet to establish the specific mode of action of these novel synthetic chalcones, it is clear from the DNA-laddering that the induction of apoptosis mediates their cytotoxic activity.

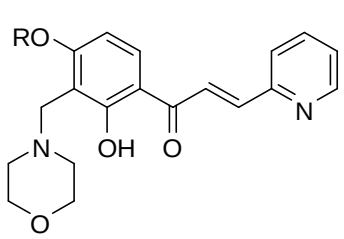
The introduction of nitrogen into molecules *via* the Mannich reaction has led to a large number of biologically active compounds. Dimmock and co-workers reviewed the anticancer properties of Mannich bases[97] and found a plethora of properties such as antimalarial[98,99], antiviral[100], antifungal[101], antibacterial[102] and other activities.[103] A full discussion of these activities is out of the scope of this thesis.

Although chalcone derivatives bearing hydroxyl, methoxy and/or methyl functions in the aryl rings have been designed as potential cytotoxic agents[104,105], little interest has been shown in the development of chalcones with nitrogen containing substituents. The conversion of various acyclic conjugated styryl ketones e.g. chalcones, into the corresponding Mannich bases often showed increased bioactivity both *in vitro* and *in vivo*.[97]

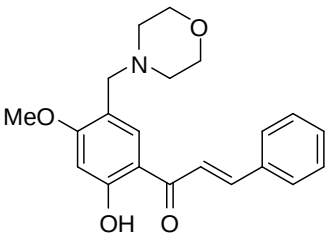
In 2008, Reddy *et al.*,[64] reported the synthesis and *in vitro* biological evaluation of heterocyclic nitrogen containing chalcones with different substitution patterns in the B-ring, together with a discussion of structure-activity relationships. Their analogs were tested for cytotoxic activity against PC-3 (prostate cancer), MCF-7 (human breast cancer), KB (nasopharyngeal carcinoma), and KB-VIN (vincristine-resistant KB subline).

The most potent compounds were **28** and **29** (Figure 1.21) with IC_{50} values of 0.08 and 0.03 µg/mL, respectively, against the MCF-7 cell line.

[97]Dimmock, J. R.; Kumar, P. *Current Med. Chem.* **1997**, *4*, 1.
[98]Barlin, G. B.; Jiravinya, C.; Yan, J. H. *Aust. J. Chem.* **1991**, *44*, 677.
[99]Barlin, G. B.; Jiravinya, C. *Aust. J. Chem.* **1990**, *43*, 1175.
[100]Edwards, M. L.; Ritter, H. W.; Stemerick, D. M.; Stewart, K. T. *J. Med. Chem.* **1983**, *26*, 431.
[101]Pandeya S. N.; Sriram, D.; Nath, G.; De Clercq, E. *Sci. Pharm.* **1999**, *67*, 103.
[102]Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. *Eur. J. Pharm. Sci.* **1999**, *9*, 25.
[103]Chaturvedi, S. C. *Indian J. Pharm. Sci.* **1985**, *17*, 155.
[104]Lawrence, N. J.; McGown, A. T.; Ducki, S.; Hadfield, J. A. *Anti-Cancer Drug Des.* **2000**, *15*, 135-141.
[105]Shibat, S. *Stem Cells* **1994**, *12*, 44-52.



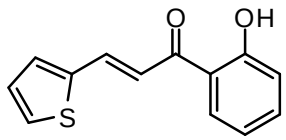
28



29

Figure 1.21: Designed target compounds synthesized by Reddy and co-workers.

Won and co-workers[106] synthesized (*E*)-1-(2-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **30**, a chalcone derivative, which was tested *in vitro* for its inhibitory activity on chemical mediators released from neutrophils, mast cells and microglial cells with satisfactory results.[107]



30

Figure 1.22: Structure of (*E*)-1-(2-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **30**.

Amodiaquine **3**, a Mannich base derivative, is a clinically used antimalarial. Mannich bases exibit antifungal properties against mycosis and dermatophytal infections. Mannich bases have been explored as prodrugs since the hydrochloric salt of the Mannich base of carbamazepine (anticonvulsant) with dipropylamine was found to be more than 10^4-fold more soluble in water than the parent drug.

[106]Won, S. J.; Liu, T-C. T.; Tsao, L. T.; Weng, J. R.; Ko, H. H.; Wang, J. P.; Lim, C. N. *Eur. J. Med. Chem.* **2005**, *40*, 103.
[107]Kouskoura, M.; Hadjipavlou-Litina, D.; Giakoumakou, M. *Med. Chem.* **2008**, *4*, 586-596.

1.3 Drug Discovery and Drug Development

Drug discovery and development is a complex process. Many bioactive compounds are toxic and thus unsuitable to be further developed into drugs. Another important issue is bioavailability. Oral bioavailability (F%) is defined as the fraction of an orally administrated drug that reaches systemic circulation.[108] High oral bioavailability reduces the amount of an administrated drug necessary to achieve a desired pharmacological effect and therefore could reduce the risk of side-effects and toxicity.

The broader criteria used to identify a possible new drug are referred to as ADME-Tox. This refers to the **a**bsorption, **d**istribution, **m**etabolism, **e**xcretion and toxicity of a pharmaceutical compound in the body. Most molecules which show bioactivity in initial bioavailability screenings, fail due to unsatisfactory ADME-Tox properties. The first hurdle is usually toxicity which refers to the fact that healthy cells are also destroyed in the process. A further problem is that the bioavailable compound never reaches the diseased organ. To address these problems; ADME-Tox protocols were developed. A full discussion of this topic is beyond the scope of this thesis.

The process of drug discovery and drug development is represented by a funnel-effect as seen in Figure 1.23. Many chemical compounds are seen as potential drugs, but few are recognized as lead candidates and only one or two of these are ultimately registered as a drug.

[108]Navia, M. A.; Chaturvedi, P. R. *Drug Discovery Today* **1996**, *1*, 179-189.

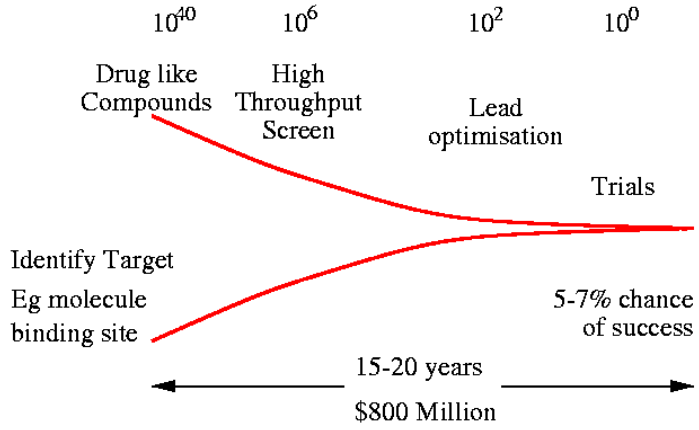
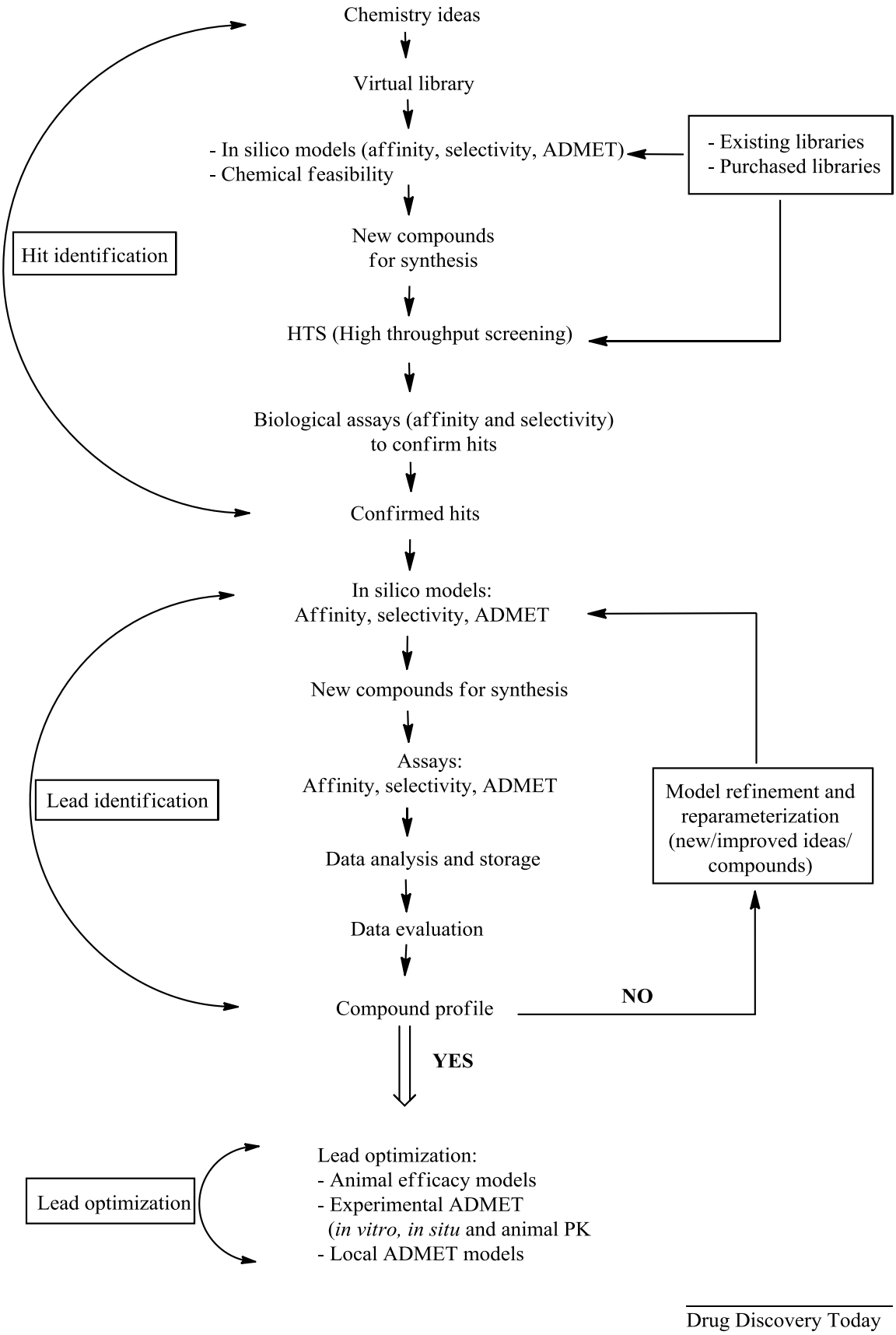


Figure 1.23: Estimated time, cost and success rate in the discovery of a drug to treat a disease.[109]

As a potential drug moves down the funnel, the cost escalates. The later a potential drug is abandoned, the more money is lost in the process. Most pharmaceutical companies now rely on computational chemistry (page 71) which can predict certain pitfalls with potential drugs before money is invested in the project. The workflow responsible for this funnel effect is summarized in Scheme 1.5.

[109]Moore, R. Mathematics Department, Macquarie University, Sydney, 1999.



Scheme 1.5: A typical workflow for a drug discovery project.[103]

1.3.1 Oral bioavailability, drug-like properties and the Lipinski rules

The pharmaceutical industry noticed during the 1990s, that many compounds were terminated in clinical development due to unsatisfactory bioavailability and pharmacokinetics (PK).[110] It became clear that the relationship between structure and PK properties has to be assessed during lead optimization.

This led to the development of empirical criteria which compounds had to meet in order to be called 'drug-like'[111,112] and to successfully pass through the development process.[88]

Lipinski's Rule of **five** evaluates drug likeness or determines if a chemical compound is likely to exhibit the specific biological activity to make it an orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997.[113]

According to Lipinski's rule, an orally active drug should not violate more than one of the following criteria:

- Not more than **5** hydrogen bond donors (nitrogen or oxygen atoms with more than one hydrogen atom)
- Not more than **10** hydrogen bond acceptors (nitrogen and oxygen atoms)
- Molecular mass less than **500**
- An octanol-water partition coefficient[114] *C*log*P* not greater than **5**

Low molecular weight has long been thought to favour compound performance.[115] The increased absorption of compounds with low molecular mass (M_r) and a suitable *C*log*P* appear to be the two physicochemical parameters which best determine oral absorption potential by passive processes according to Navia.[116] Low M_r also lessens the risk of high

[110]Kola, I.; Landis, J. *Nat. Rev. Drug Discov.* **2004**, *3*, 711-715.
[111]Sugiyama, Y. *Drug Discov Today* **2005**, *10*, 1577-1579.
[112]Sirois, S.; Hatzakis, G.; Wei, D.; Du, Q.; Chou, K. C. *Comput. Biol. Chem.* **2005**, *29*, 55-67.
[113]Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3-26.
[114]Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71 (6)*, 525-616.
[115]Barlow, D.; Satoh, T. *J. Controlled Release* **1994**, *29*, 283-291.
[116]Navia, M. A.; Chaturvedi, P. R. *Drug Discovery Today* **1996**, *1*, 179-189.

clearance since such molecules are unlikely to be substrates for hepatic clearance mediated *via* metabolism.[116] The logarithm of the octanol:water (or other lipid:water) partition coefficient (*C*log*P*) is the one physicochemical parameter used in the prediction and/or estimation of absorption potential of drugs.[114] Compounds with a high *C*log*P* (>6) display low absorption due to their poor aqueous solubility whereas compounds with suboptimal lipophilicity (*C*log*P*<-3) are unable to penetrate membrane barriers.[116] A higher *C*log*P* value tends to favour absorption across the gastrointestinal tract wall, although it renders compounds more susceptible to metabolism and biliary clearance.

All numbers are multiples of five, hence the rule of five. Like all other rules, the rule of Lipinski also has an exception to the rule. Compound classes that are substrates for biological transporters are exceptions. According to Lipinski and co-workers[113] some drugs will lie outside the parameter cut-offs in the rule. These orally active therapeutic classes outside the "rule of 5" are: antibiotics, antifungals, vitamins and cardiac glycosides. They suggest that these few therapeutic classes contain orally active drugs that violate the "rule of 5" because members of these classes have structural features that allow the drugs to act as substrates for naturally occurring transporters. Lipinski associated these physiocochemical parameters with acceptable aqueous solubility and intestinal permeability which comprise the first steps in oral bioavailability.

The rule-of five (RO5) was created as a predictor due to medicinal and combinatorial chemistry producing a high volume of compounds with poor physicochemical properties. Failing the RO5 predicted oral activity problems; although passing the RO5 was no guarantee that a compound was drug-like. Citations in CAS Scifinder to the original rule-of-five publication[117] in 1997 and its reprint in 2001 exceeded 1000 by the end of 2004.

The Comprehensive Medicinal Chemistry (CMC), Derwent Word Drug Index (WDI) and Modern Drug Data Report (MDDR) are among the more commonly used drug-like databases.[118,119]

[117]Lipinski, C. A. *et al*., *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25.
[118]Oprea, T. I. *J. Comput. Aided Mol.* **2000**, *14*, 251-264.
[119]Bradley, M. P. *Mol. Divers.* **2002**, *5*, 175-183.

The Lipinski rules are based on empirical observations of passively absorbed drugs and do not apply to actively absorbed drugs. The rules are thus not absolute and other factors may be involved in regard to oral bioavailability. These include molecular flexibility for membrane permeation, the negative impact of a high polar surface area on intestinal absorption[120] and the unfavorable property of water complexation by amide bonds.[121]

Egan *et al*.[122] suggested that drug absorption is sufficiently encoded in lipophilicity plus polar surface area, without explicit reference to molecular weight.

1.3.2 Prodrugs

The concept of "prodrug" was first introduced by Adrian Albert in 1958 to describe compounds that undergo biotransformation prior to eliciting their pharmacological effect. The prodrug itself is thus not biologically active and is metabolized in the blood to a biologically active compound. It is a well established strategy to improve the physicochemical, and/or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the developability and usefulness of a potential drug.

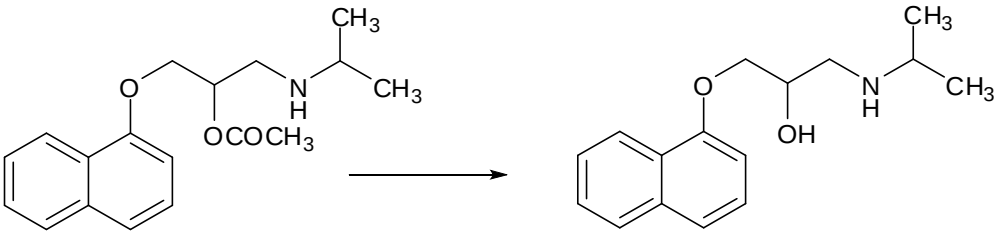
Many drugs exhibit limited systemic bioavailability due to first-pass metabolism which reduces the drug concentration before it reaches systemic circulation. This is often seen in drugs bearing the phenolic hydroxyl group. This pitfall can be avoided by administering the drug orally as a prodrug to minimize metabolism and to ensure that the conversion of the prodrug does not occur in the intestine or the liver.[123]

The prodrug approach to drug design is a versatile and powerful method that can be applied to a wide range of drug administration routes and formulations for many types of parent drug molecule. Analysis of parent-drug properties and the proper identification of barriers are crucial for successful prodrug strategies. A major aim is to prevent first pass metabolism[124] and to deliver a higher concentration of the pharmacologically active drugs into the systemic

[120]Clark, D. E. *J. Pharm. Sci.* **1999**, *88*, 807-814.
[121]Hirschmann, R. *J. Med. Chem.* **1997**, *40*, 2440-2444.
[122]Egan, W. J.; Merz, K. M.; Baldwin, J. J. *J. Med. Chem.* **2000**, *43*, 3867-3877.
[123]Svensson L. A.; Tunek, A. *Drug Metab. Rev.* **1988**, *19*, 165-194.
[124]Ettmayer, P.; Amidon, G. L.; Clement, B.; Testa, B. *J. Med. Chem.* **2004**, *47*, 393.

circulation.

By incorporating one of the simplest acyl groups such as the acetate group, the prodrug *O*-acetylpropranolol **31** (Figure 1.24) yielded higher blood levels of propranolol **32**, by side-stepping the first-pass metabolism of the parent drug in the liver as observed by Anderson in 1988.[125]



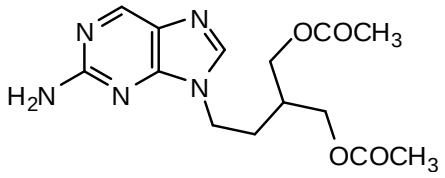
Prodrug **Active drug**

31 **32**

Figure 1.24: Chemical structure of the prodrug *O*-acetylpropranolol **31** and the active drug, propranolol **32**.

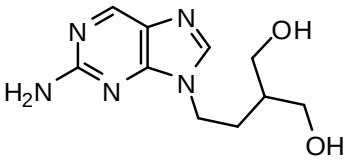
The use of diesters as the promoiety was also investigated in the case of famciclovir **33** (Figure 1.25), the orally administered diacetate ester prodrug of the antiviral agent penciclovir **34** as described by Filer and co-workers.[126] An absolute bioavailability of penciclovir **34** of 77% was seen following oral administration and high absorption of famciclovir **33**. The latter is rapidly and extensively metabolized by hydrolysis of the esters and oxidation at C-6 to yield penciclovir **34** which reaches peak plasma concentration within 45 minutes.

[125]Anderson, B. D.; Chu, W. W.; Galinsky, R. E. *Int. J. Pharm*. **1988**, *43*, 261-265.
[126]Filer, C. W.; Allen, G. D.; Brown, T. A.; Fowles, S. E.; Hollis, F. J.; Mort E. E.; Prince, W. T.; Ramji, J. V. *Xenobiotica* **1994**, *24*, 357-368.



Prodrug

33

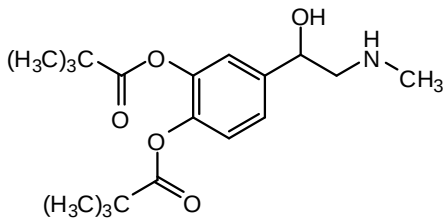


Active drug

34

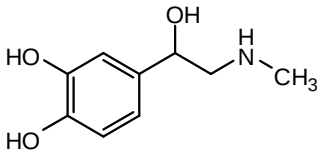
Figure 1.25: Chemical structure of famciclovir **33** and penciclovir **34**.

Branched acyl groups as promoieties have been investigated due to their increased lipophilicity and slower chemical and enzymatic hydrolysis compared to their linear analogues. Hussain and co-workers proved this theory with dipivefrine **35** (Figure 1.26) (the dipivalic acid diester of epinephrine), which penetrates the cornea 17 times faster than epinephrine **36** (Figure 1.26) due to its 600-fold higher lipophilicity at pH 7.2.[127]



Prodrug

35



Active drug

36

Figure 1.26: Structure of dipivefrine **35** and epinephrine **36**.

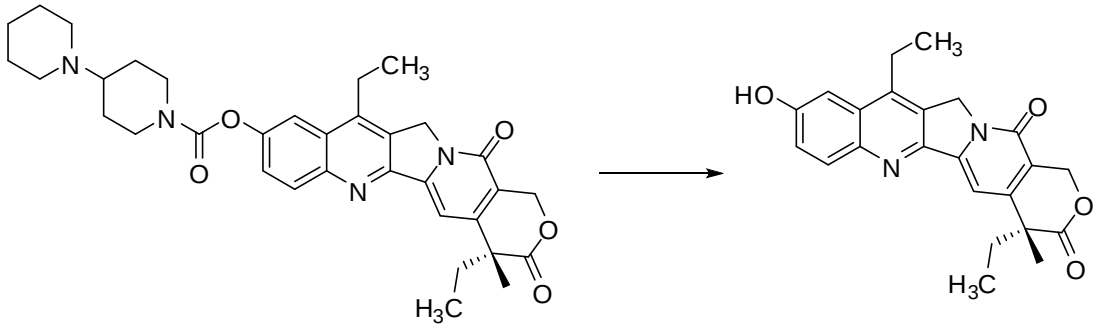
Preventing first pass metabolism and increasing bioavailability is not the only reason for prodrugs.

The best known prodrug is aspirin. It is a derivative of salicylic acid that limits damage to the stomach.

Prodrugs of hydroxyl-containing anticancer drugs have been used for site-spesific activation where the prodrug can differentiate between normal and cancer cells by metabolic differences

[127]Hussain, A.; Truelove, J. E. *J. Pharm. Sci.* **1976**, *65*, 1510-1512.

between the two. One such an example is Irinotecan hydrochloride trihydrate **37** (Figure 1.27) (Camptosar®, Pfizer) which is a prodrug of SN-38 **38** (Figure 1.27) with a 1000-fold potency over irinotecan *in vitro* as an inhibitor of type-I DNA topoisomerase.[128]



Prodrug **Active drug**

37 **38**

Figure 1.27: Cleavage of the ester bond in irinotecan **37** by means of human liver microsomal carboxylesterases, CES1A1 and CES2, releasing the piperidinopiperidine promoiety and SN-38 **38**, the active form of the drug.[129]

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[128]Kunimoto, T.; Nitta, K.; Tanaka, T.; Uehara, N.; Baha, H.; Takeuchi, M.; Yokokura, T.; Sawada, S.; Miyasaka, T.; Mutai, M. *Cancer Res.* **1987**, *47*, 5944-5947.

[129]Slatter, J. G.; Su, P.; Sams, J. P.; Schaaf, L. J.; Wienkers, L. C. *Drug Metab. Dispos.* **1997**, *25*, 1157-1164.

2 Results and discussion

Antimalarial and anticancer properties of novel aminoalkylated chalcones and analogues

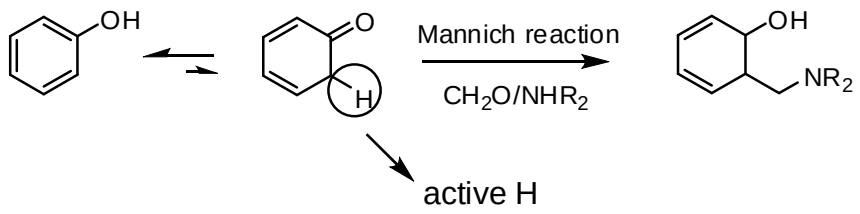
2.1 Synthesis and antimalarial screening

This project was initiated with the hypothesis that introducing nitrogen into a flavonoid molecule would improve the bioactivity of the molecule. A further consideration was that flavonoids are usually not bioavailable due to their polyphenolic nature. We thus embarked on a project to synthesize nitrogen containing flavonoids with a minimum number of hydroxyl groups. Chalcones are probably the most readily synthetically available flavonoids. We thus initiated our project with the syntheses of a series of nitrogen containing chalcones by performing the Mannich reaction on the chalcones.

The Mannich reaction involves the condensation of a CH-activated compound (usually an enolizable aldehyde or a ketone) with a primary or secondary amine (or ammonia) and a non-enolizable aldehyde (or ketone) to afford aminoalkylated derivatives[130,131] This reaction has been reviewed by Blicke,[132] Karbe,[133] Thompson[134] and many others.

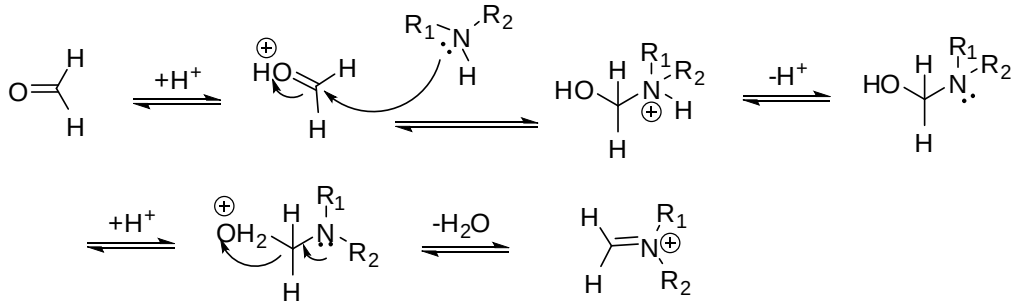
The Mannich reaction requires an active hydrogen atom. This reaction can thus be applied to aromatic rings provided one hydroxyl group is available in the *ortho*-position. The *ortho*-hydrogen is active in the enol form as seen in Scheme 2.1. Due to the requirement of an active hydrogen, all our aminoalkylated chalcones contain an aromatic OH *ortho* to the aminoalkyl moiety.

[130]Waring, A. J. *Comprehensive Organic Chemistry, Vol. 1,* Pergamon Press, Oxford, 1979, 1041.
[131]Mannich, C.; Krosche, W. *Arch. Pharm*. **1912**, *250*, 647.
[132]Blicke, F. F. *In; Organic Reactions.Vol.1,* John Wiley and Sons, New York; 1942, 303.
[133]Karbe, H. *Arch. Pharm.* **1950**, *283*, 38.
[134]Thompson, B. B. *J. Pharm. Sci*. **1968**, *57*, 715.



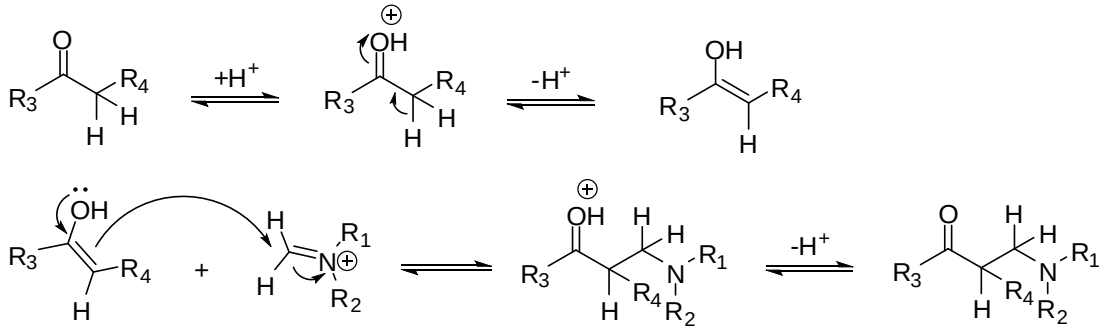
Scheme 2.1: Active phenol o*rtho*-hydrogen *via* the enol form followed by the Mannich reaction.

The mechanism of the Mannich reaction can proceed under both acidic and basic conditions, although acidic conditions are more common (Schemes 2.2 and 2.3).



Scheme 2.2: Formation of the reactive iminium ion under acidic conditions.

The compound with the carbonyl functionality can tautomerize to the enol form, after which it can attack the iminium ion (Scheme 2.3).



Scheme 2.3: Aminoalkylation of the enolized carbonyl compound.

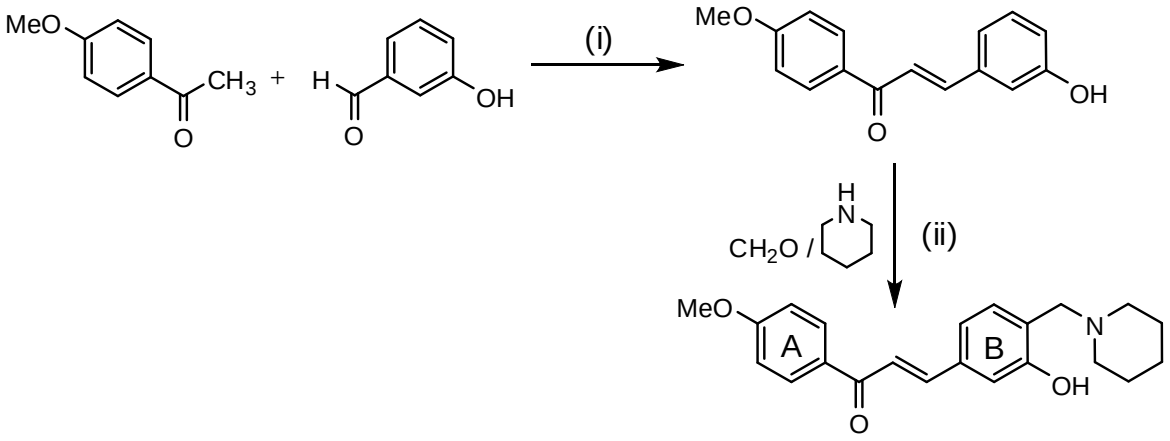
The resulting aminoalkylated chalcones were subjected to malaria and cancer *in vitro*

bioactivity testing. We tested the more promising candidates for toxicity with CHO[135] (Chinese hamster ovarian) and HeLa[136] (Human Negroid cervix epitheloid adenocarcinoma) cell lines *in vitro* and calculated selectivity indices (SI). More details of the bioactivity and toxicity testing are given on pages 93–98 and in Appendix B. Some of our most promising molecules were submitted to *in vivo* mice antimalarial assays and feedback from this assay, including bioavailability data, were used to design further analogues. The mice assays and bioavailability determinations were part of a separate PhD project by Mr Efrem Techlehaymanot Abay.[137] The results are presented as follows:

- Antimalarial bioactivity of the chalcones (compounds **39** and **40**) compared to their aminoalkylated analogues (compounds **41** and **42**) (Table 2.1).
- Antimalarial bioactivity of chalcone derivatives with different amine moieties on the B-ring (Table 2.2).
- The effect of the A-ring substituents on the *in vitro* antimalarial bioactivity and RI values (Table 2.3).
- Antimalarial bioactivity of the aminoalkylated dihydrochalcone analogues and RI values (Table 2.4).
- Antimalarial bioactivity of diarylpropane analogues against chloroquine sensitive and chloroquine resistant strains and RI values (Table 2.5).
- Antimalarial bioactivity of diarylpropane analogues with different B-ring substituents (Table 2.6).
- Antimalarial bioactivity of the hydrochloric salts of the diarylpropane analogues and RI values (Table 2.7).
- Antimalarial bioactivity results on the structural modifications performed on compound **39** (Table 2.8).
- Antimalarial bioactivity of analogues with modified chain lengths (Table 2.9).
- Antimalarial bioactivity of other modifications to the initial structures (Table 2.10).

An example of our general synthetic method is given in Scheme 2.4 with piperidine as the amine moiety.

[135]Jayapal, K. P.; Wlaschin, K. F.; Yap, M. G. S.; Hu, W-S. *Chem. Eng. Prog.* **2007**, *103 (10)*, 40-47.
[136]Rahbari, R.; Sheahan, T.; Modes, V.; Collier, P.; Macfarlane, C.; Badge, R. M. *BioTechniques* **2009**, *46 (4)*, 277-284.
[137]Abay, E. T. A Pharmacokinetic and Pharmacodynamic Investigation of Potential Antimalaria Compounds in Mice, PhD Dissertation, University of the Free State, 2013.



Reagents and conditions: (i) 50% KOH-solution, EtOH, rt; (ii) EtOH & HCl reflux (9 h)

Scheme 2.4: Synthesis of an aminoalkylated chalcone *via* the Mannich reaction.

The chalcones were obtained in yields of between 60 and 80%. The Mannich reaction performed on the chalcones gave products in yields of between 75 and 90% (see Chapter 4).

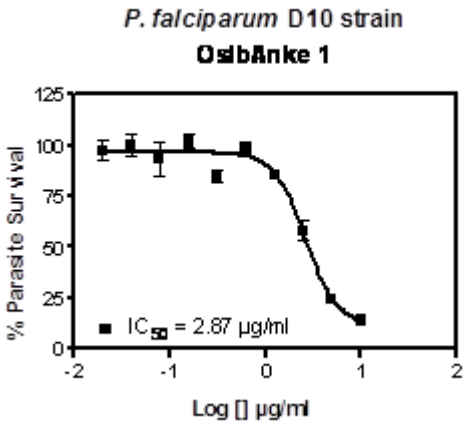
2.2 Bioactivity testing of our compounds against Malaria

Most of our bioactivity testing was directed at antimalaria bioactivity and this formed the major part of this thesis. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were available using a modified method of Trager and Jensen (page 93–94).[138] Quantitative assessment of antimalarial activity *in vitro* was determined by the University of Cape Town (UCT) *via* the parasite lactate dehydrogenase assay using a modified method described by Makler.[139] Initially the D10 plasmodium chloroquine sensitive strain[140] (CQS) was used, later to be replaced by the NF54 strain,[141] also chloroquine sensitive since UCT's project with Medicine for Malaria Venture (MMV) used the NF54 strain. The difference

[138]Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673-675.
[139]Makler, M. T.; Ries, J. M.; Williams, J. A.; Bancroft, J. E.; Piper, R. C.; Gibbins, B. L.; Hinrichs, D. J. *The American Society of Tropical Medicine and Hygiene* **1993**, *48*, 739-741.
[140]Walliker, D.; Quakyi, I. A.; Wellems, T. E.; McCutchan, T. F.; Szarfman, A.; London, W. T.; Corcoran, L. M.; Burkot, T. R.; Carter, R. *Science* **1987**, *236*, 1661-1666.
[141]Ponnudurai, T.; Leeuwenberg, A. D.; Meuwissen, J. H. *Tropical and Geographical Medicine* **1981**, *33*, 50-54.

between D10 and NF54, both chloroquine sensitive strains, are small, and results are comparable.[142] The more promising molecules were subsequently tested against chloroquine resistant strains, Dd2[143] and K1.[144] Antimalarial bioactivity testing was done according to the method on page 93–94.

The bioactivity results are expressed as IC_{50}, corresponding to the drug concentration leading to 50% parasite growth inhibition. These values were calculated from the dose response curves of the compounds involved. An example of such a curve (for compound **39**) is given in Graph 2.1. All the dose-response curves are given in Appendix B. Chloroquine was used as an internal standard to monitor the experimental conditions and showed IC_{50} values within an acceptable range (0.018–0.060 μM for the sensitive strains and 0.470–0.780 μM for the resistant strains). CHO cells were used to test the general toxicity of compounds with low IC_{50} values from the antimalarial bioactivity data. In a few cases, HeLa cell toxicity data was determined by the Council of Scientific and Industrial Research (CSIR). Toxicity values, also given as IC_{50}, were also calculated from the dose response curves, using the value where 50% of the CHO or HeLa cells were killed by the compounds involved.



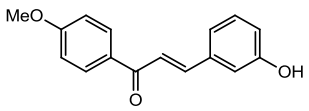
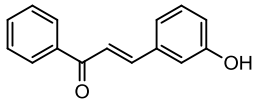
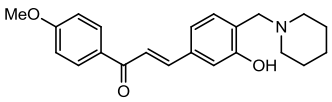
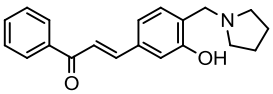
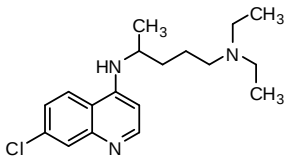
Graph 2.1: Dose-response curve of compound **39** (Table 2.1) against the CQS D10 strain of *P. falciparum.*

[142]Personal communication, Dr L. Wiesner, University of Cape Town, Cape Town, South Africa.
[143]Noedl, H.; Wongsrichanalai, C.; Wernsdorfer, W. H. *Trends Parasitol.* **2003**, *19*, 175-181.
[144]Burkot, T. R.; Williams, J. L.; Schneider, I. *Trans R. Soc. Trop. Med. Hyg.* **1984**, *78*, 339-341.

2.3 The effect of introducing an aminoalkyl moiety into a chalcone on its antimalarial activity

Our first results, summarised in Table 2.1, indicated that the introduction of an aminoalkyl group into chalcones enhanced bioactivity against the chloroquine sensitive *Plasmodium falciparum* strain, D10 by almost a ten-fold factor. These initial results support our hypothesis that the introduction of a nitrogen containing group into a chalcone, in this case *via* a piperidine or pyrrolidine containing aminoalkyl moiety, will enhance the bioactivity (compounds **41** and **42**).

Table 2.1: Antimalarial bioactivity of the chalcones (compounds **39** and **40**) compared to their aminoalkylated analogues (compounds **41** and **42**).

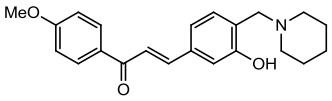
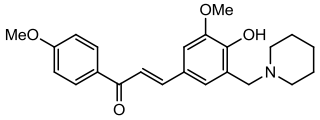
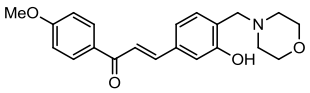
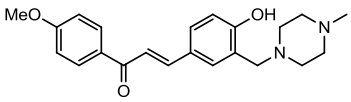
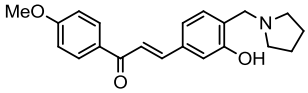
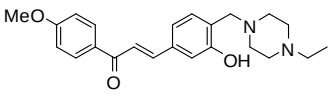
Compound	**Code**	**Structure**	**Antimalarial activity, IC_{50} D10 (µM)**
39	OslbAnke1		11.30
40	Ojvdwaw737		15.71
41	Ojvdwaw720		0.83
42	Ojvdwaw758		6.54
	Chloroquine (CQ)		0.015–0.065

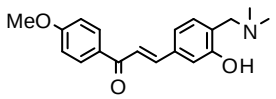
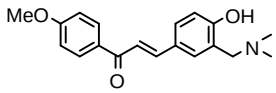
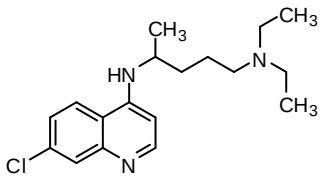
D10: Chloroquine sensitive *Plasmodium falciparum* strain

2.4 The effect of introducing different amine moieties on the B-ring

These initial results (Table 2.1), although promising, do not warrant development of compounds **39**–**42** into antimalarial drugs. The IC_{50} values were still too high and not comparable to chloroquine. We thus embarked on a project to increase the bioactivity *via* structure modifications and the synthesis of analogues. Our first strategy was to look at the influence of the amine groups in the aminoalkyl moiety. The chalcone derivatives in Table 2.2 were synthesized and tested for antimalarial bioactivity. The substituent on the A-ring (4-OMe) was kept constant. The results are given in Table 2.2.

Table 2.2: Antimalarial bioactivity of chalcone derivatives with different amine moieties on the B-ring.

Compound	Code	Structure	Antimalarial activity, $IC_{50,}$ D10 (µM)
41	Ojvdwaw720		0.83
43	Ojvdwaw722		2.81
44	Ojvdwaw723		4.90
45	OslbAnke4		3.77 (n=2)
46	Ojvdwaw743		5.75
47	Ojvdwaw744		2.74

Compound	Code	Structure	Antimalarial activity, IC_{50} D10 (µM)
48	Ojvdwaw731		2.52
49	Ojvdwaw745		>3
	CQ		0.015–0.065

n: Number of replicates

D10: Chloroquine sensitive *Plasmodium falciparum* strain

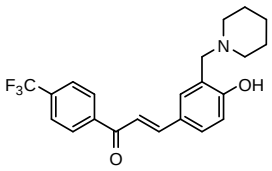
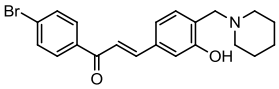
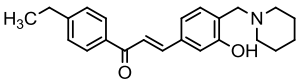
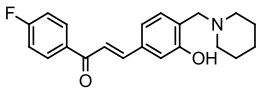
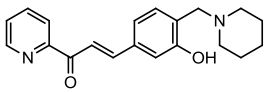
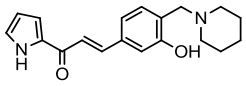
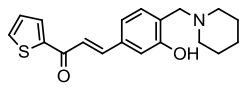
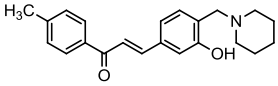
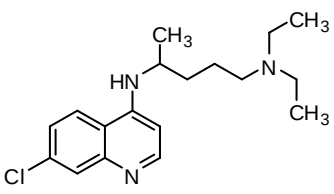
Replacing the piperidine moiety with morpholine (compound **44**), 1-methylpiperazine (compound **45**), pyrrolidine (compound **46**) and 1-ethylpiperazine (compound **47**) did not increase bioactivity significantly. We thus decided to move forward and exclusively synthesise further analogues with piperidine as the amine moiety of choice. This allowed us to keep the number of possible analogues manageable.

We did not extensively explore the influence of changing the position of the hydroxyl group or the effect of other substituents on the B-ring; however compound **43** (OMe on the 5-position) and compound **45** (OH on the 4-position) in Table 2.2 suggest that this would not have a significant effect.

2.5 The effect of modifications on the A-ring

To investigate the role of substituents on the A-ring, we synthesized a series of compounds with different A-ring substituents. Table 2.3 contains the antimalarial bioactivity of aminoalkylated chalcones with different substituents on the A-ring against chloroquine sensitive (D10) and chloroquine resistant (CQR) (Dd2) strains and RI values.

Table 2.3: The effect of the A-ring substituents on the *in vitro* antimalarial bioactivity against CQS and CQR strains and RI values.

Compound	Code	Structure	IC_{50} D10 (µM)	IC_{50} Dd2 (µM)	RI
50	NP-103		0.167	0.195	1.17
51	NP-087		0.145	0.207	1.43
52	NP-091		0.140	0.206	1.47
53	NP-038		0.097	0.713	7.35
54	NP-059		1.371	–	–
55	NP-042		2.42	–	–
56	NP-044		2.73	–	–
57	NP-072		>3	–	–
	CQ		0.015–0.065	0.225–0.474	

D10: Chloroquine sensitive *Plasmodium falciparum* strain

Dd2: Chloroquine resistant *Plasmodium falciparum* strain

RI: Resistance index – IC_{50} Dd2/IC_{50} D10

As indicated in Table 2.3 (compounds **50**–**53**) the substituents on the A-ring do have an influence on the bioactivity, especially when the methoxy group (as in Table 2.2) on the 4-position was replaced with CF_3, Br, F and CH_2CH_3. The IC_{50} values of some of our analogues (e.g. compound **53**, where OMe was replaced with F) showed another 10-fold increase in bioactivity from the previous increase of almost 10-fold from Table 2.1. Since we now have increased the bioactivity by almost a factor 100 compared to the original non-nitrogen containing chalcone, we introduced Dd2, the chloroquine resistant *Plasmodium falciparum* strain, into our bioassay. Compounds **50**–**52** with the best antimalarial bioactivity against the chloroquine sensitive (D10) strain, showed similar activity to CQ against the chloroquine resistant (Dd2) strain.

This suggests that aminoalkylated chalcones use a different parasite inhibitory mechanism than chloroquine which usually has an RI value of between 5 and 10.

2.6 The effect of removing the enone system on bioactivity

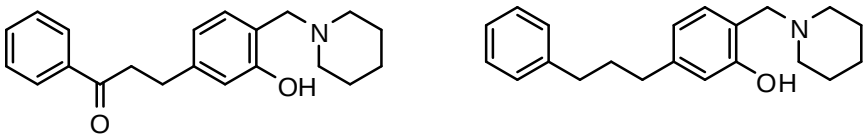
After discussions with a medicinal chemist (Dr Chris Edlin from iThemba Pharmaceuticals) we decided to change the enone system to a propyl system *via* catalytic hydrogenation for the following reasons:

- It would enhance bioactivity. This is due to removal of the rigidity associated with the conjugated double bond. It is generally assumed by medicinal chemists that reducing the aromatic characteristics, gives a more flexible molecule, which will fit more easily into active sites in the enzymes.[145,146,147]
- It is generally assumed that an enone system is readily metabolized in the blood and removal of the enone system would enhance bioavailability.[145,146,147]

[145]Leeson, P.; St-Gallay, S. *Med. Chem. Commun.* **2011**, *2*, 91-105.
[146]Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756.
[147]Ritchie, T. J.; Macdonald, S. J. F. *Drug Discov. Today* **2009**, *14*, 1011-1020.

- Enone systems are associated with increased toxicity and carcinogenicity due to their ability to alkylate DNA *via* conjugated nucleophilic addition.

We thus aimed to produce the partially hydrogenated dihydrochalcones (**58**) and fully hydrogenated diarylpropanes (**59**) as shown in Figure 2.1 and their analogues.

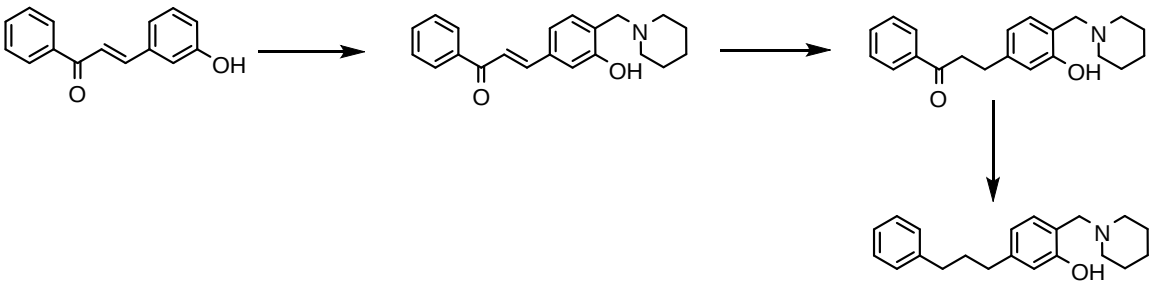


58 **59**

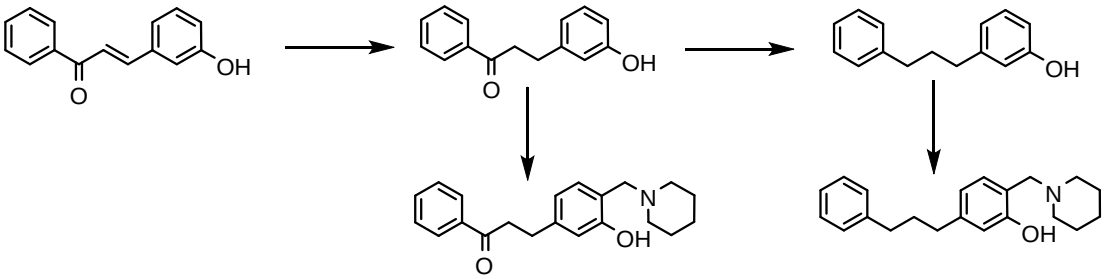
Figure 2.1: Structural backbone of dihydrochalcone (**58**) and diarylpropane (**59**).

Two strategies to obtain the desired dihydrochalcone and diarylpropane analogues were investigated:

1. Synthesis of the alkylaminochalcone followed by selective and exhaustive hydrogenation (Scheme 2.5).
2. Synthesis of the dihydrochalcone and diarylpropane molecules followed by the Mannich reaction (Scheme 2.6).

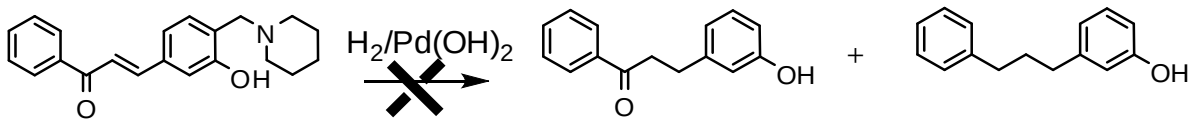


Scheme 2.5: Synthesis of an aminoalkylated chalcone followed by hydrogenation.



Scheme 2.6: Synthesis of a dihydrochalcone and diarylpropane followed by the Mannich reaction.

Hydrogenation of the aminoalkylated chalcones gave undesired products in low yield. Instead of the formation of the desired aminoalkyldihydrochalcones and -diarylpropanes, only products where the aminoalkyl groups had been lost, were isolated in low yields (5–10%) (Scheme 2.7).



Scheme 2.7: Failed synthesis represented in Scheme 2.5.

The second strategy of performing the Mannich reaction on partially or fully hydrogenated dihydrochalcones or diarylpropanes gave excellent yields, both in the hydrogenation step and the aminoalkylation step. Yields ranged between 80 and 90% for the dihydrochalcones and in excess of 90% for the diarylpropanes.

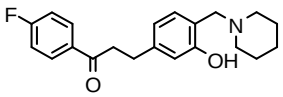
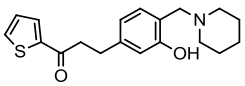
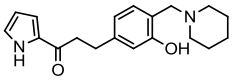
Salient is the fact that yields of the aminolalkylation steps of both the dihydrochalcone and diarylpropane were much higher than those obtained upon aminoalkylation of the chalcones. The non-conjugated B-ring is thus more reactive as a nucleophile in the Mannich reaction than a conjugated B-ring. Removal of conjugation probably increased the energy of the highest occupied π-ring orbital and thus nucleophilicity.

The ratio between partially and fully reduced chalcones could be controlled by the reaction time of hydrogenation (24–48 h vs. 48–72 h) and the reaction conditions. Initially we hydrogenated under a pressure of 20 bar, but this is a potentially dangerous route to follow since working under such high pressure may cause explosions and requires constant monitoring to maintain optimum pressure. We subsequently discovered that catalytic hydrogenation at atmospheric pressure in the presence of small amounts of acid (10% aq. HCl), gave the desired products. The aminoalkylated dihidrochalcone (overnight stirring) and the aminoalkylated diarylpropane (48–72 h stirring) were obtained in good yields (>90%).

The carbonyl group on chalcone-type compounds with heterocyclic A-rings, particularly those with nitrogen and sulfur, was rather resistant to hydrogenation and could not be

obtained *via* catalytic hydrogenation. This was attributed to conjugation of the carbonyl with the lone electon-pair on the sulfur and nitrogen atoms of the heterocyclic A-ring. By using NH_2-NH_2 and KOH/NaOH[148] the desired diarylpropanes were obtained. Antimalarial bioactivity results of the dihydrochalcones are given in Table 2.4.

Table 2.4: Antimalarial bioactivity of the aminoalkylated dihydrochalcone analogues and RI values.

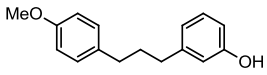
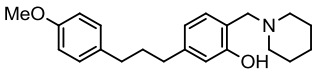
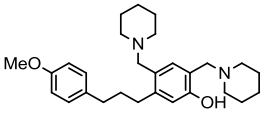
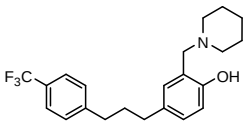
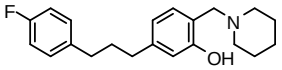
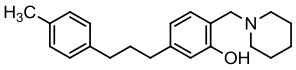
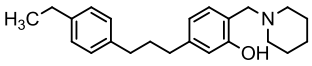
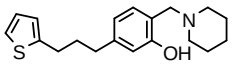
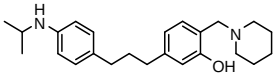
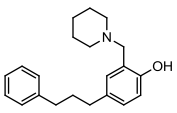
Compound	**Code**	**Structure**	**IC_{50} D10/NF54 (μM)**	**IC_{50} Dd2 (μM)**	**RI**
60	Pravin.K116		0.263 (NF54)	–	–
61	NP-054		0.188 (D10)	0.273	1.45
62	NP-045		>3 (D10)	–	–

Dihydrochalcones did not show an increase in bioactivity compared to the chalcone precursors. Since the IC_{50} values in Table 2.4, did not show an increase in bioactivity when comparing for example, compound **60** (0.263 μM) with compound **53** (0.097 μM) (Table 2.3). Compound **61** (0.188 μM) was an exception when compared to compound **56** (2.73 μM) from Table 2.3. The novel heterocyclic nitrogen containing A-ring did not give improved results. We therefore did not proceed to synthesise more dihydrochalcone analogues.

The fully reduced diarylpropanes however gave very promising results and we ventured forward in our quest for improved bioactivity by synthesizing an array of fully reduced diarylpropanes as seen in Table 2.5. The chloroquine resistant strain K1 was introduced for the first time in Table 2.5. As previously explained in the case of D10 and NF54, there are minor genetic differences between Dd2 and K1, but the results are considered similar.[142]

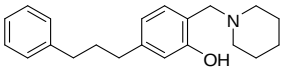
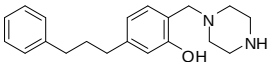
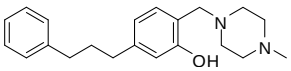
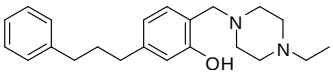
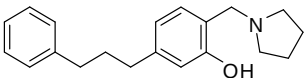
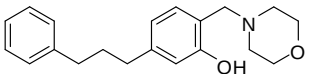
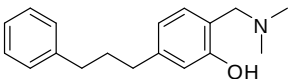
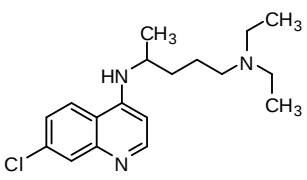
[148]Zhang, Z.; Zhang, L.; Guan, X.; Shen, Z.; Chen, X.; Xing, G.; Fan, X.; Zhou, Q. *Liquid Crystals* **2010**, *37*, 69-76.

Table 2.5: Antimalarial bioactivity of diarylpropane analogues against CQS and CQR strains and RI values.

Com-pound	Code	Structure	IC_{50} D10/NF54 (µM)	IC_{50} K1/Dd2 (µM)	RI
63	Ojvdwaw738		>30 (D10)	–	–
64	Ojvdwaw742		0.21 (n=2) (D10)	–	–
65	Ojvdwaw750		0.057 (D10)	0.084 (Dd2)	1.47
66	NP-102		0.005 (D10)	0.029 (Dd2)	5.8
67	NP-046		0.069 (D10)	–	–
68	NP-074		0.089 (D10)	0.272 (Dd2)	3.06
69	NP-085		0.182 (NF54)	–	–
70	Pravin.K077		0.050 (NF54)	0.024 (K1)	0.48
71	Pravin.K065		0.184 (NF54)	–	–
72	NP-0119		0.060 (NF54)	–	–

The low value of compound **63** compared to compound **39** suggests that non nitrogen containing chalcone antimalarial bioactivity has to do with the enone moiety.

Table 2.6: Antimalarial bioactivity of diarylpropane analogues with different B-ring substituents.

Compound	Code	Structure	IC_{50} D10/NF54 (µM)	IC_{50} K1/Dd2 (µM)
73	NP-036		0.138 (NF54)	–
74	NP-0106		2.81 (NF54)	–
75	NP-0107		0.787 (NF54)	–
76	NP-0108		0.405 (NF54)	–
77	NP-0112		0.041 (NF54)	–
78	NP-0113		0.745 (NF54)	–
79	NP-0114		0.093 (NF54)	–
	CQ		0.015–0.065	0.225–0.474

In order to retest our assumption that piperidine as the amine group gives the most active

analogues, based on chalcones with a methoxy group on the A-ring (Table 2.2), we synthesized the fully reduced analogues (diarylpropanes) with different amine moieties. The results indicated that in the case of diarylpropanes, pyrrolidine (compound **77**) is a slightly more active moiety than piperidine (compound **73**).

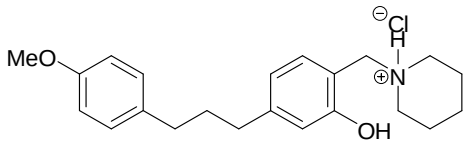
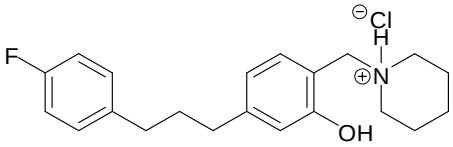
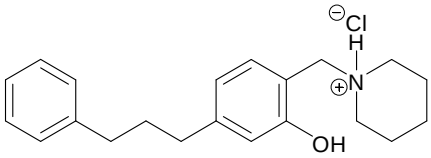
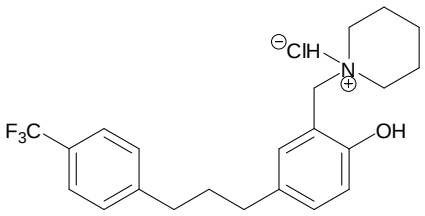
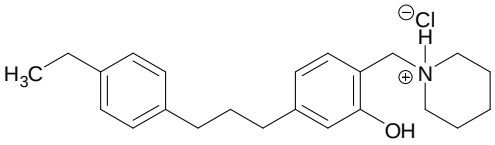
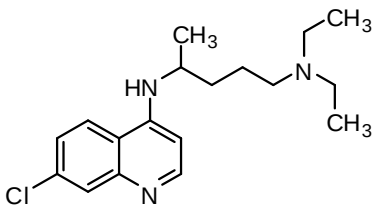
There seems to be a relationship between planarity and drug-likeness. Lovering and co-workers[146] found that molecules with a higher degree of saturation and more chiral centres have lower melting points, higher solubility and a better chance of clinical success. This correlates with our own finding that removal of the enone moiety enhances bioactivity.

Our assumption that the removal of rigidity in our molecule caused by the enone system would lead to increased bioactivity, proved to be true as seen in the exceptionally increased bioactivity results in Table 2.5 (by another factor 10 when focusing on compound **66**). We saw excellent increases in bioactivity in the fully reduced diarylpropanes in Table 2.5 when compared to our initial aminoalkylchalcones in Table 2.1.

2.7 The effect of the salts of the diarylpropanes on bioactivity

Some of our compounds were not soluble in the solvents used for the *in vitro* bioactivity determinations, method development for the bioanalytical quantification of our compounds in blood samples, and the anticipated mice *in vivo* bioavailability determinations. We thus made hydrochloric acid salts to enhance solubility. This was easily achieved by bubbling dry HCl gas through a solution of the free amine containing aminoalkylated compounds. NMR was used to establish that all chemical shifts had changed during salt formation and that no free amine resonances remained. The *in vitro* bioactivity results are given in Table 2.7. The quantification and subsequent mice bioavailability results formed part of another PhD thesis,[137] but are referred to in section 2.10 of this chapter.

Table 2.7: Antimalarial bioactivity of the hydrochloric salts of the diarylpropane analogues against CQS and CQR strains and RI values.

Com-pound	Code	Structure	IC_{50} D10/NF54 (µM)	IC_{50} K1/Dd2 (µM)	RI
80	Ojvdwaw742 (salt)		0.069 (D10)	0.069 (Dd2)	1.00
81	NP-046 (salt)		0.028 (n=6) (D10)	0.022 (Dd2)	0.79
82	NP-036 (salt)		0.023 (n=6) (D10)	0.031 (Dd2)	1.35
83	NP-102 (salt)		0.277 (NF54)	–	–
84	NP-085 (salt)		0.062 (NF54)	–	–
	CQ		0.015–0.065	0.225–0.474	

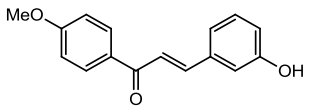
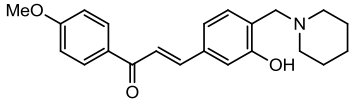
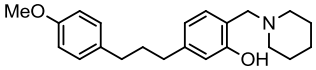
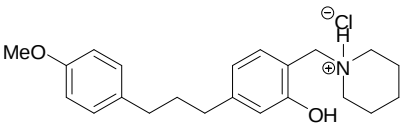
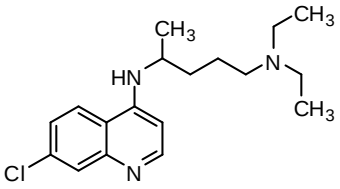
By comparing Table 2.5 (bioactivity of free amines) with Table 2.7 (amine hydrochloric salts) it is clear that salt formation does not interfere with the *in vitro* bioactivity and in fact enhances it for most of the compounds. It is assumed that the enhanced polarity and solubility assist transport across cell membranes. The three RI values available (compounds **80**, **81** and **82**) suggests, taken the biological variability inherent in our screen into account, that our compounds have the same activity against chloroquine sensitive and chloroquine resistant malaria strains. These compounds thus use a different mechanism of action compared to chloroquine.

Summary of results so far

Table 2.8 showcases the stepwise increase in antimalarial bioactivity of analogues of compound **39** as they were modified from an aminoalkylated chalcone, to a fully reduced diarylpropane and subsequently to the salt of the diarylpropane. We have thus succeeded in preparing chalcone analogues with antimalarial bioactivity that is comparable to chloroquine in sensitive strains and far exceeding that of chloroquine in resistant strains. Our compounds thus have the promise of antimalarial drugs, provided that bioavailability and toxicity is acceptable which was indeed the case as seen in Tables 2.11 and 2.13.

It must be kept in mind that our bioassays are based on living cells. Our IC_{50} results are thus not absolute and some variation in results can be expected as the bioassay is not always exactly the same. This is evident from the ranges in IC_{50} values obtained for CQ for both the sensitive and resistant strains.

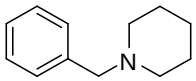
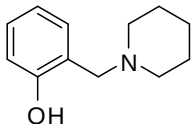
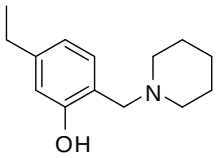
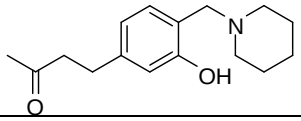
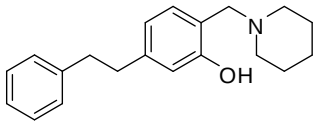
Table 2.8: Antimalarial bioactivity results on the structural modifications performed on compound **39**.

Com-pound	Code	Structure	IC_{50} D10/NF54 (µM)	IC_{50} K1/Dd2 (µM)
39	OslbAnke1		11.30	–
41	Ojvdwaw720		0.83	–
64	Ojvdwaw742		0.21 (n=2) (D10)	–
80	Ojvdwaw742 (salt)		0.069 (D10)	0.069 (Dd2)
	CQ		0.015–0.065	0.225–0.474

2.8 The effect of the chain length on bioactivity

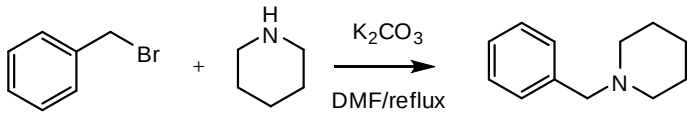
To establish whether the aminoalkyl phenol moiety on its own would be bioactive and whether the arylpropane extension moiety was indeed necessary for antimalarial activity the analogues in Table 2.9 were synthesised and tested in the antimalarial bioassays.

Table 2.9: Antimalarial bioactivity of analogues with modified chain lengths.

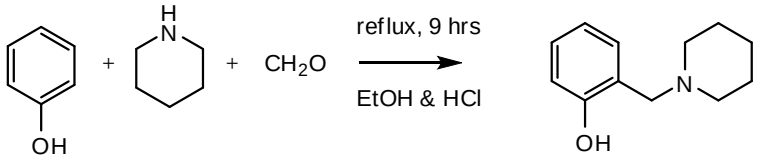
Compound	Code	Structure	IC_{50} NF54 (µM)	IC_{50} K1/Dd2 (µM)
85	Pravin.K049		>5	–
86	Pravin.K105		>5	–
87	Pravin.K040		1.044	–
88	Pravin.K022		1.711	–
89	Pravin.K034		0.115	–

The aminoalkyl benzene and aminoalkyl phenol (compounds **85** and **86**) showed no bioactivity. Interestingly, the addition of an ethyl group (compound **87**) introduced bioactivity, albeit not in the same league as our promising compounds. The same applies to the diarylethane analogue (compound **89**), synthesized *via* a Wittig reaction (Scheme 2.12). Due to time constraints and the fact that none of the entries in Table 2.9 showed improved activity compared to the corresponding diarylpropane analogues; we did not pursue the effect of chain length any further.

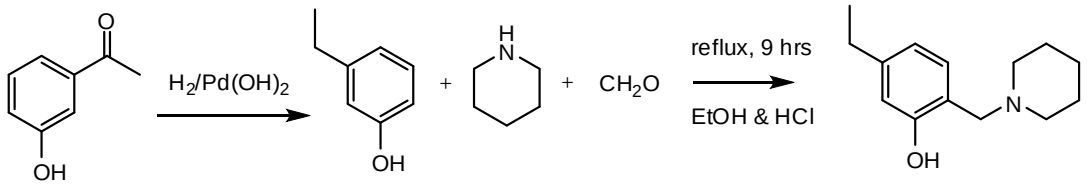
Compound **85** was synthesized according to the reaction given in Scheme 2.8. Compound **86** was obtained from reacting phenol with piperidine (Scheme 2.9) according to the general procedure for the Mannich reaction given in the experimental section (Chapter 4). Compound **87** was obtained by hydrogenation followed by the Mannich reaction (Scheme 2.10).



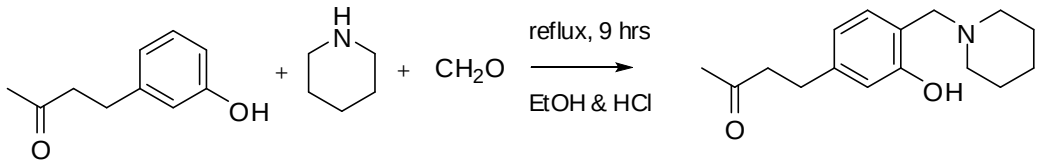
Scheme 2.8: Reaction conditions for the synthesis of compound **85** from Table 2.9.[149]



Scheme 2.9: Synthesis of compound **86** *via* the Mannich reaction.



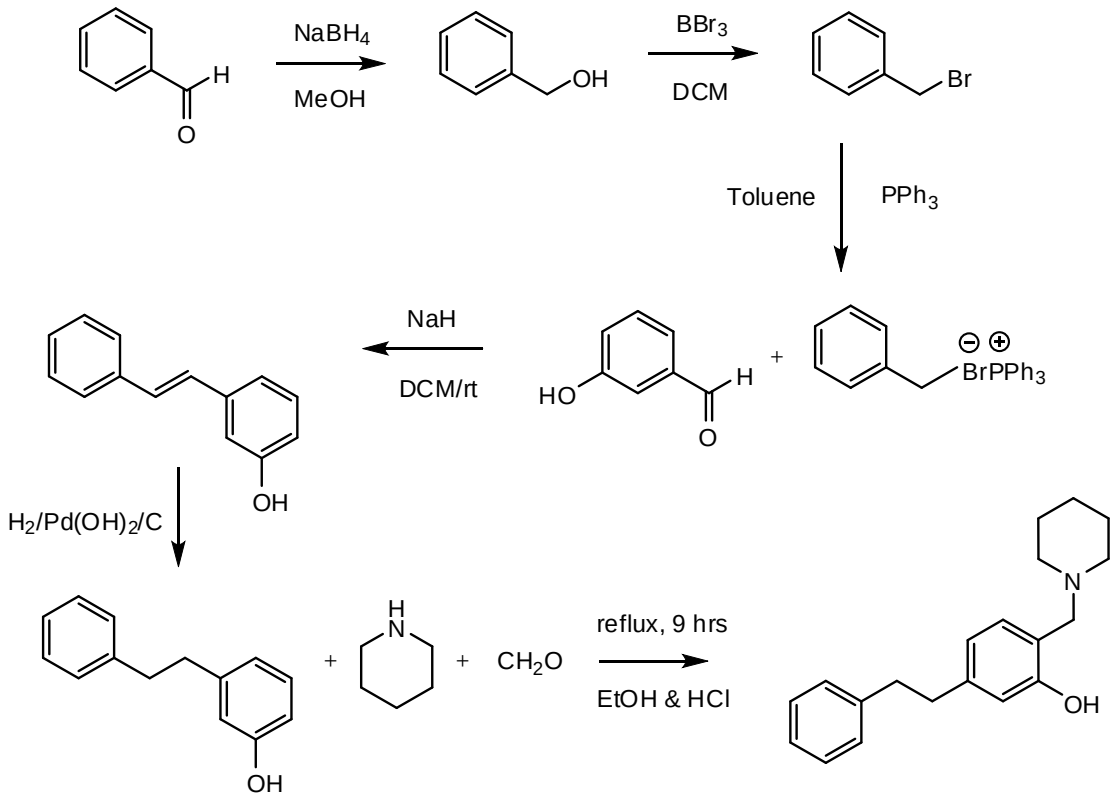
Scheme 2.10: Synthesis of compound **87** from Table 2.9 *via* the Mannich reaction.



Scheme 2.11: Synthesis of compound **88** from Table 2.9 *via* the Mannich reaction.

Compound **88** was synthesized via the Mannich reaction as seen in Scheme 2.11. Compound **89**, the diarylethane analogue, was synthesized *via* a Wittig reaction as shown in Scheme 2.12, followed by hydrogenation and the Mannich reaction to obtain the final product.

[149]Awasthi, S. K.; Mishra, N.; Kumar, B.; Sharma, M.; Bhattacharya, A.; Mishra, L. C.; Bhasin, V. K. *Med. Chem. Res.* **2009**, *18*, 407.420.

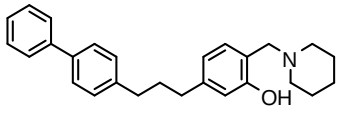
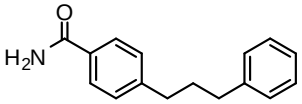
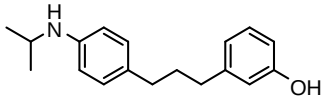
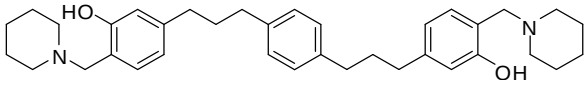
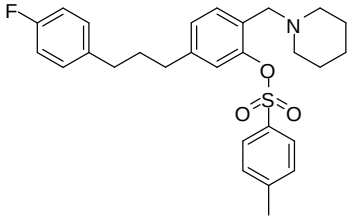
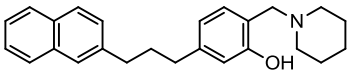


Scheme 2.12: Synthesis of the diarylethane analogue (compound **89**) *via* the Wittig reaction.

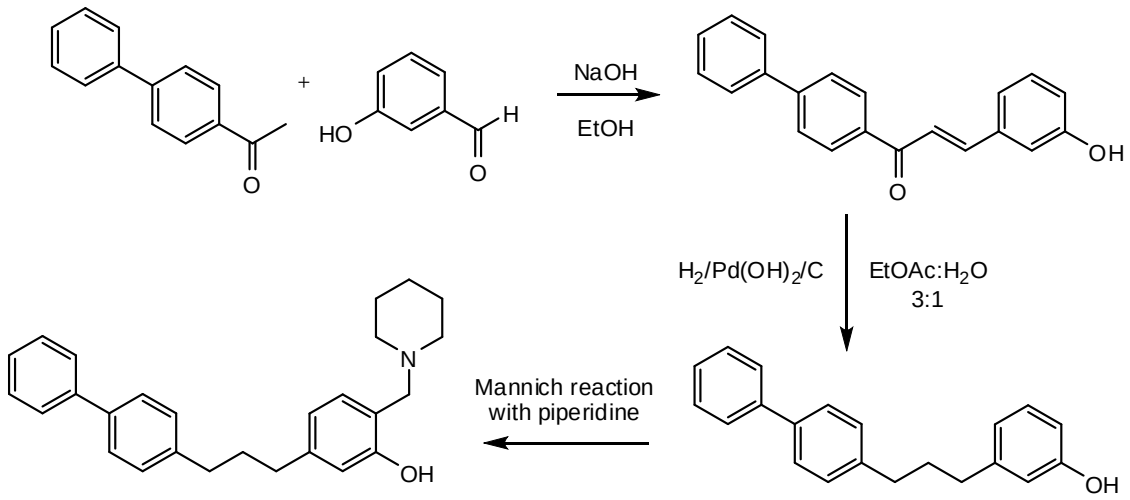
2.9 The effect of other chalcone analogues on bioactivity

During our investigation a number of nitrogen containing diarylpropanes were synthesized that did not fit into the above tables and classifications. These analogues with their bioactivity are given in Table 2.10.

Table 2.10: Antimalarial bioactivity of other modifications to the initial structures.

Compound	Code	Structure	IC_{50} NF54 (µM)
90	Pravin.K115		0.076
91	Pravin.K05		>4
92	Pravin.K064		>3
93	Pravin.K057		0.064
94	Pravin.K063		>2
95	NP-0123		0.044

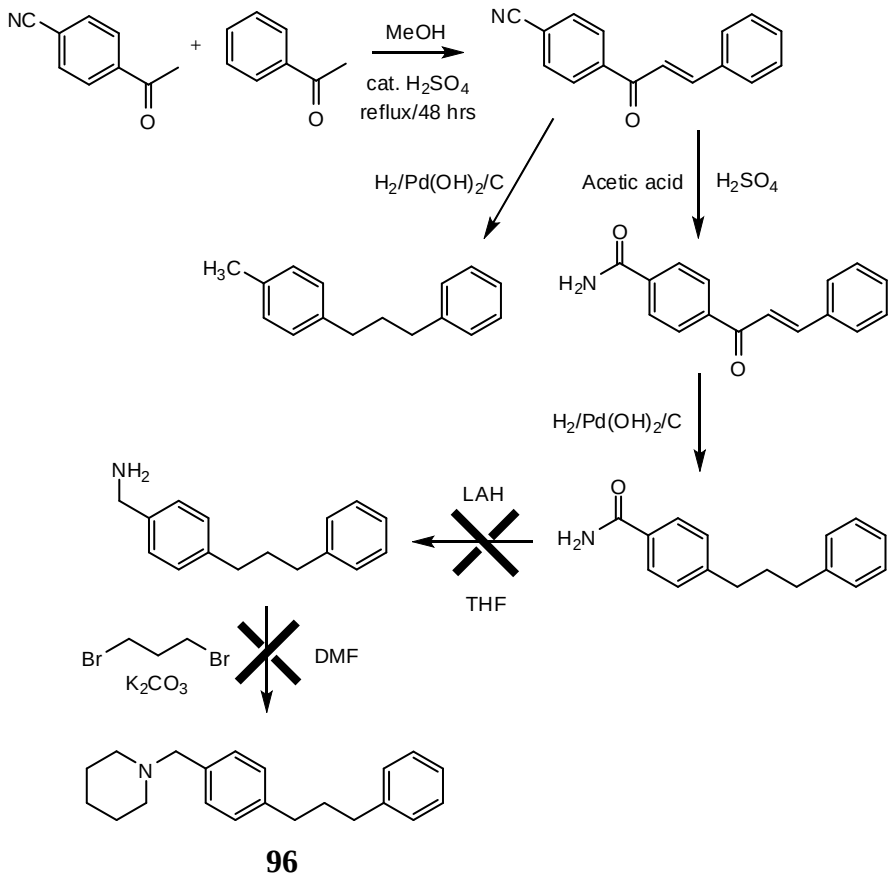
Compound **90**, the biphenylic analogue, was synthesized *via* the procedure given in Scheme 2.13. The good bioactivity indicated that modifications on the A-ring of the diarylpropanes might lead to enhanced bioactivity.



Scheme 2.13: Synthesis of compound **90**, the biphenylic analogue.

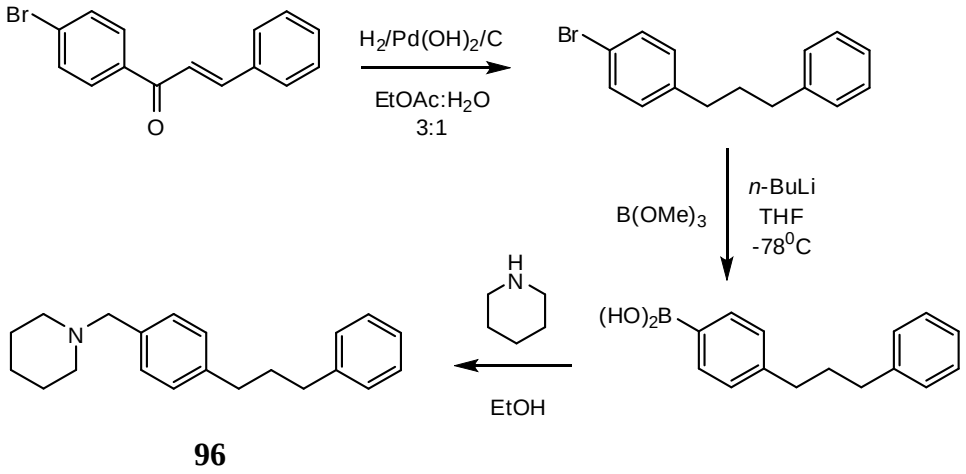
Compound **91** was synthesised in an effort to obtain an aminoalkyl diarylpropane without an *ortho* OH group to establish whether the OH-moiety on the B-ring was necessary (Scheme 2.14). This synthesis failed and due to time constraints was not further pursued. Work is in progress to synthesise compound **96** from Scheme 2.14 *via* the Petasis Boronic acid-Mannich reaction (Scheme 2.15).[150]

[150]Kliś, T.; Serwatowski, J.; Wesela-Bauman, G.; Zadrożna, M. *Tetrahedron Letters* **2010**, 51, 1685 – 1689.



96

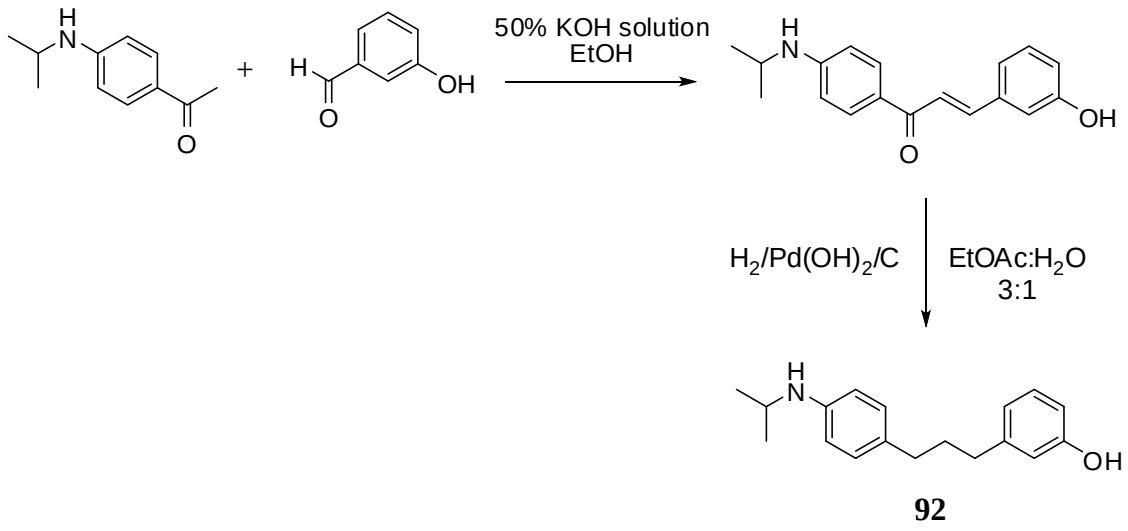
Scheme 2.14: Failed synthesis of diarylpropane analogue without an *ortho* OH group.



96

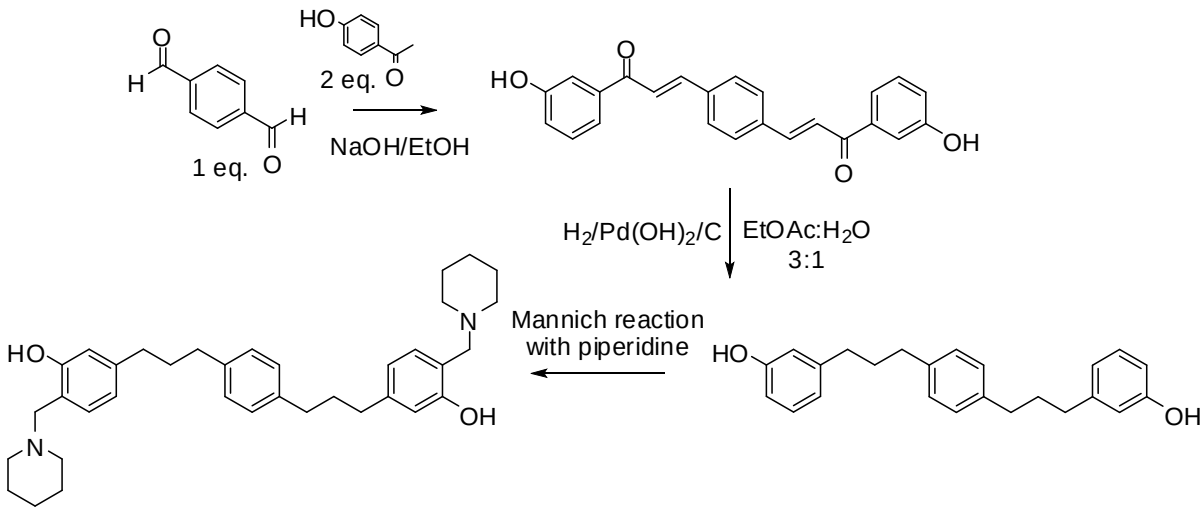
Scheme 2.15: Proposed synthesis for compound **96** *via* the Petasis Boronic acid-Mannich reaction.

The low bioactivity of compound **92** suggests that either the aminoalkyl moiety (a CH_2 linkage between the aromatic ring and the amine group) or an *ortho* OH is essential (Scheme 2.16). Of particular interest is compound **93**, a molecule with two diarylpropane moieties, which was synthesised according to Scheme 2.17. This compound may have increased bioavailability as two phenol groups have to be metabolized *in vivo* before the reactive moiety is deactivated.



92

Scheme 2.16: Synthesis of compound **92**.



93

Scheme 2.17: Synthesis of compound **93**, the two diarylpropane analogue.

The low activity of compound **94** suggests that the *ortho* OH is essential. This compound is

currently being investigated with *in vivo* mice experiments as a potential prodrug (Scheme 2.18). Compound **95** suggests that large moieties on the A-ring will not reduce bioactivity. This is supported by compounds **66** (CF_3), **68** (CH_3) and **69** (CH_2CH_3) in Table 2.5 and compounds **99** and **100** in Table 2.12.

2.10 Bioavailability

Bioavailability is an essential component in any drug development programme. Many promising drug leads have low bioavailability and are thus not further developed into commercial oral drugs.

A major concern was that the *ortho*-OH group, prescribed by the Mannich reaction's requirement of an active hydrogen, would lower bioavailability due to first-pass metabolism (degradation in the liver immediately after absorption from the intestines). Phenol containing compounds are notorious for their low bioavailability and many prodrug strategies have been developed to overcome first-pass metabolism of phenol containing drugs.[151] For example, aspirin is a prodrug of salicylic acid. This fear was justified by the 2.9% bioavailability determined for compound **80**, in the HCl salt form (Mr Abay's thesis)[137] (Table 2.11, page 66). This prompted us to synthesise analogues with either no OH group or with the OH group protected. As seen later in Table 2.11 analogues with a more hydrophobic A-ring also showed enhanced bioavailability.

In a prodrug strategy the OH would be protected and only unmasked after the protecting group has been removed *via* metabolism in the blood, usually during first-pass metabolism. Our initial efforts to protect the *ortho* OH however unexpectedly failed. Despite our best efforts, we could not make the simple acetate esters (acetic anhydride/pyridine, even with DMAP catalysis), or methoxy ethers (diazomethane or methylsulfate/potassium carbonate). We attribute this to an intramolecular hydrogen bond between the OH hydrogen and the aminoalkyl nitrogen *via* a stable six membered ring (Figure 2.2).

[151]Dhareshwar, S. S.; Stella, V. J. *Biotechnology: Pharmaceutical Aspects* **2007**, *5*, 731-799.

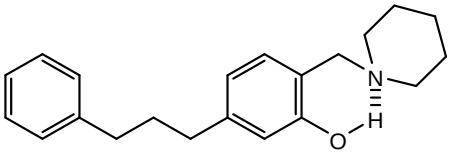
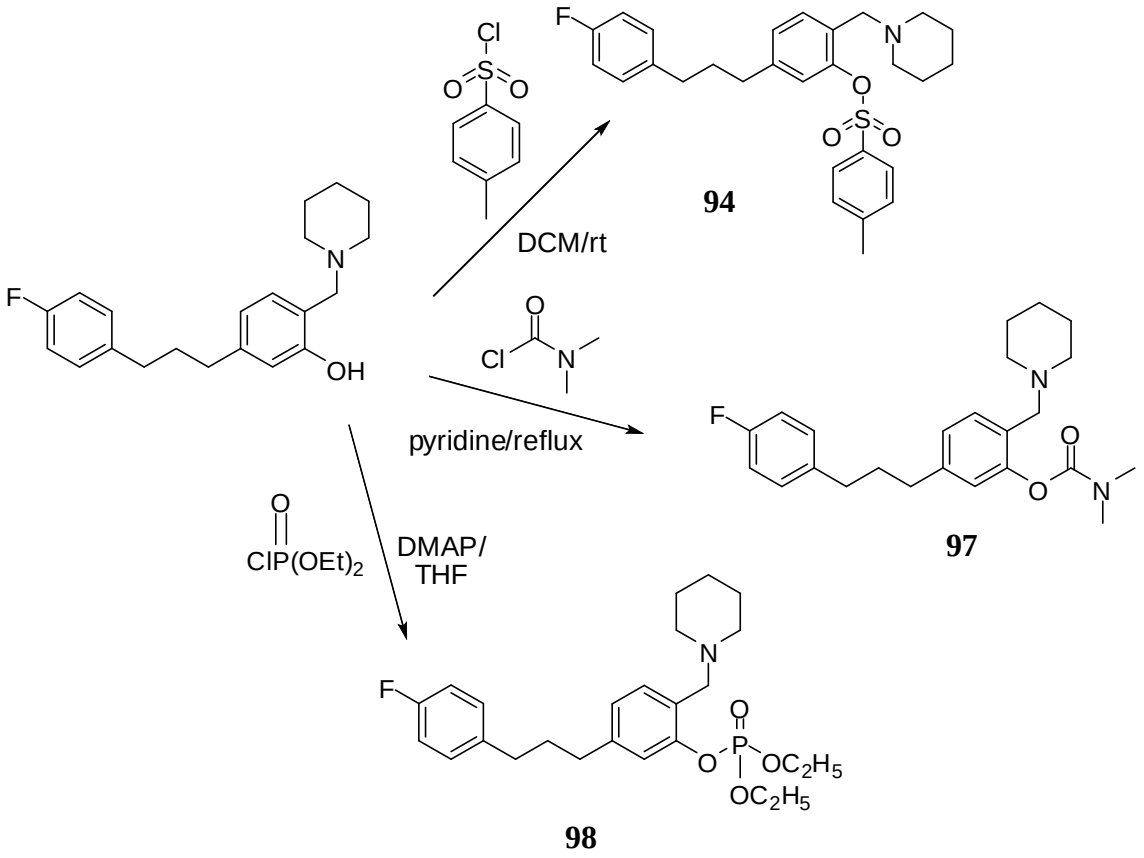


Figure 2.2: Intramolecular hydrogen bond between the OH hydrogen and the aminoalkyl nitrogen.

We subsequently succeeded to synthesise a number of potential prodrugs as seen in Scheme 2.18. The bioactivity results for compounds **97** and **98** are being awaited. Bioavailability determinations are not part of this thesis, but we will continue to synthesise potential prodrugs once results are obtained. Bioavailability requires larger amount of material (ca. 50 mg) for the *in vivo* mice experiments as compared to the *in vitro* cell based activity testing (ca. 5 mg)

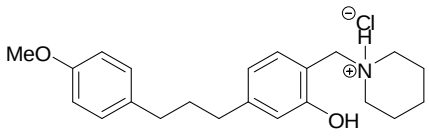
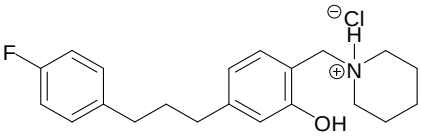
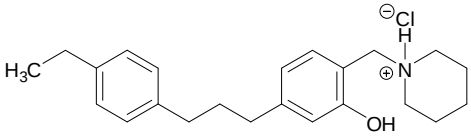
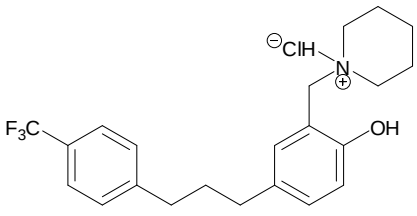


Scheme 2.18: Synthesis procedure for the potential prodrugs (compounds **94**, **97** and **98**).

We were however surprised to observe that when we replaced the 4-fluoro substituent in the

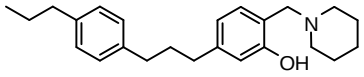
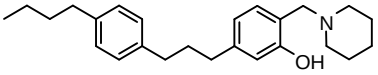
compound that we submitted for bioavailability testing (compound **81**) with a 4-ethyl group (compound **84**), bioavailability increased from 3 to 7% (Table 2.11). This suggested that groups on the A-ring could enhance bioavailability and protect the OH group on the B-ring against first-pass metabolism. This can probably be explained by the lock and key model where large substituents on the A-ring prevent our molecule to fit in the enzyme, thus protecting the OH *via* steric factors. Replacing the ethyl group with a CF_3 group (compound **83**) and placing the OH group on the 4-position increased bioavailability to 25% (Table 2.11). Although 25% is still a relatively low number, many commercial drugs have similar bioavailability. Furthermore formulation, including microencapsulation, may increase bioavailability. Interestingly, compound **83** with *C*Log*P* outside the Lipinski range of <5, gave the best bioavailability.

Table 2.11: Bioavailability of selected analogues and *C*Log*P* values of their free amines.

Compound	**Code**	**Structure**	**Bioavailability (%)**	***C*Log*P* (free amines)**
80	Ojvdwaw742 (salt)		2.9	5.370
81	NP046 (salt)		3.0	5.477
84	NP085 (salt)		7.0	6.228
83	NP0102 (salt)		25.0	6.209

We have thus embarked on a programme to synthesize a number of analogues with large substituents on the A-ring (Table 2.12). Establishing their bioavailability is in progress.

Table 2.12: Antimalarial bioactivity of analogues with a large group on the A-ring.

Compound	Code	Structure	IC_{50} NF54 (µM)	IC_{50} K1/Dd2 (µM)
99	Pravin.K0140		0.162	–
100	Pravin.K0141		0.106	–

Our research group thus has a two pronged approach to further increase bioavailability, a prodrug strategy where the *ortho* OH is protected and a large A-ring substituent approach with the OH group left unprotected. The success of the prodrug strategy not only depends on our ability to synthesise potential prodrugs, but also on the ability of enzymes in the body to remove the protecting group after or during first-pass (from the intestines through the liver). The large A-ring approach also relies on our ability to manufacture analogues with large substituents on the A-ring, but also assume that these substituents will interfere with first-pass metabolism *via* steric factors.

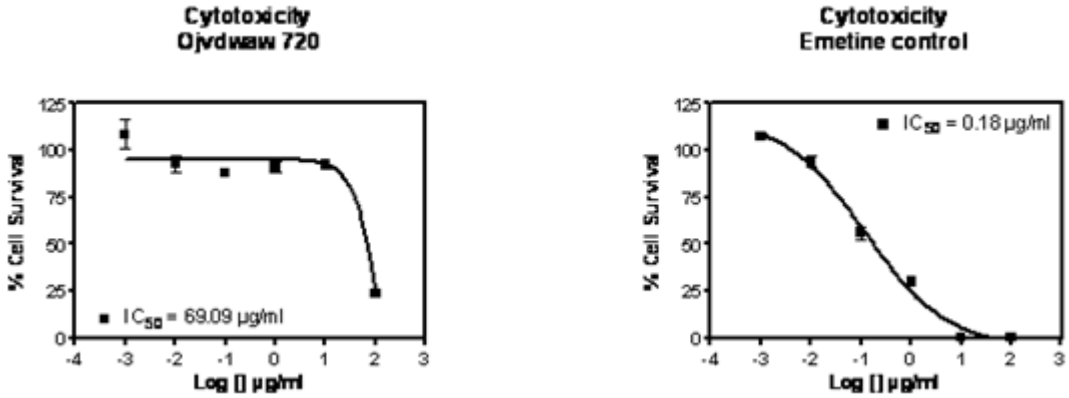
2.11 Toxicity

Paracelsus, sometimes referred to as the father of toxicology, already remarked in the fourteenth century that “All things are poison, and nothing is without poison; only the dose permits something not to be poisonous".[152] Compounds with antimalarial activity that also kill normal cells at the same concentration required to kill malaria cells are therefore poisons. We thus determined the toxicity of a representative sample of our compounds and calculated a selectivity index (SI). The results are summerised in Table 2.13 on page 69.

[152]Madea, B.; Muβhoff, F.; Berghaus, G. *DeutscherÄrzte-Verlag* **2007**, 435.

It is rather difficult to test for toxicity in *in vitro* screens as it is difficult to keep normal human cells alive. The CHO cell line is currently used as a substitute for normal human cells and is derived from Chinese hamster ovarian cells. This is considered as a satisfactorily initial model for toxicity against normal human cell lines and a prerequisite for more elaborate toxicity testing prior to clinical trials. The cytotoxicity IC_{50} value of the compound is determined in a similar way to the antimalarial IC_{50} value from the dose-respone curves and is divided by the antimalarial IC_{50} value to obtain the malarial selectivity index (SI) value. The selectivity index values were determined for each compound, using the D10/NF54 strain. Details of the test are given on page 95.

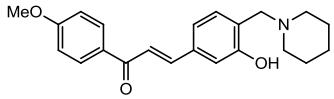
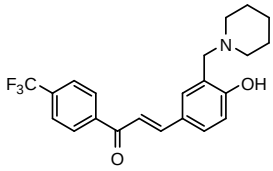
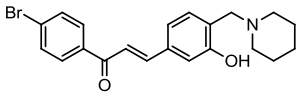
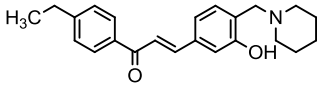
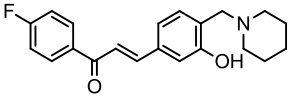
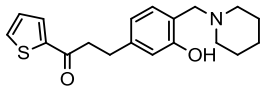
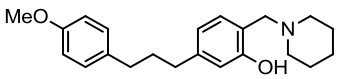
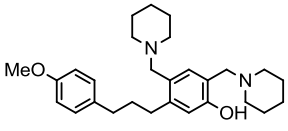
Toxicity IC_{50} values were obtained from the dose-response curves. Graph 2.2 gives an example of such a curve for compound **41**.

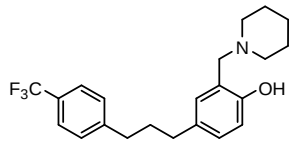
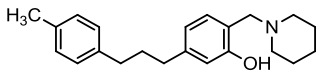
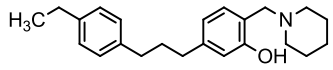
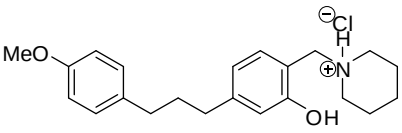
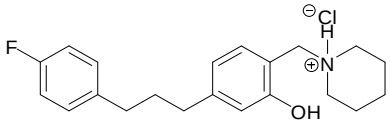
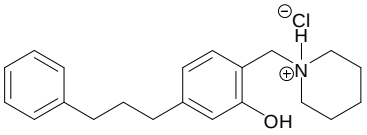
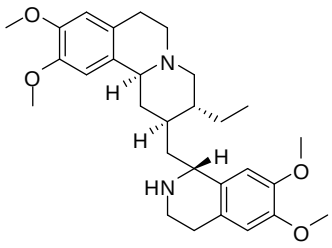


Graph 2.2: Dose-response curves of compound **41** and emetine against the CHO cell-line

Emetine was used as a quality control standard to monitor the experimental conditions and showed IC_{50} values within an acceptable range (0.08–0.12 µM).

Table 2.13: Toxicity values (IC_{50}) of our most promising analogues against CHO cell lines and SI values.

Compound	Structure	IC_{50} D10/NF54(µM)	CHO toxicity (µM)	SI
41		0.83 (D10)	196.74	237
50		0.167 (D10)	8.22	49
51		0.145 (D10)	7.27	50
52		0.140 (D10)	6.59	47
53		0.097 (D10)	77.25	796
61		0.188 (D10)	168.32	895
64		0.21 (D10)	69.84	332
65		0.057 (D10)	200.08	3510

Compound	Structure	IC_{50} D10/NF54(µM)	CHO toxicity (µM)	SI
66		0.005 (D10)	23.06	4612
68		0.089 (D10)	4.95	56
69		0.182 (NF54)	25.2	138
80		0.069 (D10)	211.35	3063
81		0.028 (D10)	163.28	5831
82		0.023 (D10)	161.65	7028
Emetine			0.03–0.50	

SI: Selectivity index = IC_{50}CHO/IC_{50} D10

From Table 2.13 we conclude that some of our more promising compounds have high selectivity indices and are thus promising drug leads, not only from a bioactivity point of view, but also from a toxicity perspective.

The most active compounds showed relatively low cytotoxicity and the selectivity index value indicates that these compounds selectively inhibit parasites compared to healthy cells. These compounds fit well within the selectivity criteria set by Pink and co-authors and are therefore considered good candidates for further animal testing.[153]

2.12 Computational chemistry and drug-like properties

Quantitative Structure-Activity Relationships (QSAR) calculations have become popular to predict the structure of potentially bioactive molecules and analogues as targets for synthesis and bioactivity testing. Most biologically active molecules act *via* enzyme inhibition or activation at a so-called active site in the enzyme. If this site is known, from X-ray crystallography of enzymes in the crystallized form, other sources of information like the three dimensional structure of a potential inhibitor or activator (ligands) that will dock in these positions, can theoretically be calculated. QSAR calculations have however not proven to be the holy grail of drug discovery and many compounds that were supposed to be very active, based on QSAR predictions, proved to be inactive. However, QSAR calculations are widely used and the time may be ripe to investigate QSAR calculations to further enhance the bioactivity of our most promising molecules. Taking the knowledge that we have accumulated so far in an effort to calculate the three dimensional structure of the active site involved and identifying the enzyme. Our research team will explore collaborations with experts that have the required expertise and calculating power.

As discussed in the literature survey, many compounds that are bioactive and non-toxic in *in vitro* studies fail in *in vivo* experiments and are never developed into commercial drugs. This is attributed to bioavailability and related issues. Lipinski studied the molecular properties of commercially available drugs and published the 'so called' Lipinski rules. These are empirical rules that have become very influential in predicting bioavailability and are now extensively used. However, exceptions do exist and the rules should be used with caution. The rules do not apply to intravenous drugs. The rules can be summarized as follows:

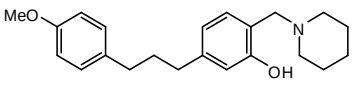
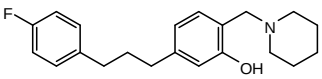
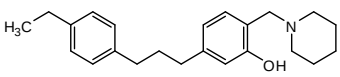
[153] Pink, R.; Hudson, A.; Mouriés, M. A.; Bendig, M. *Nature Reviews* **2005**, *4*, 727-740.

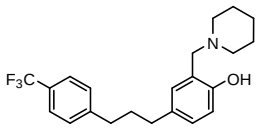
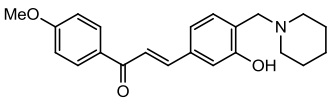
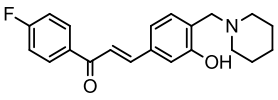
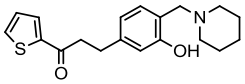
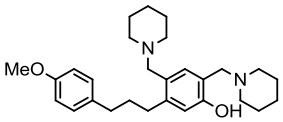
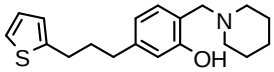
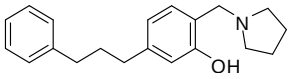
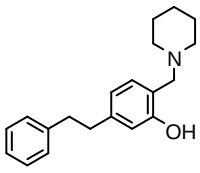
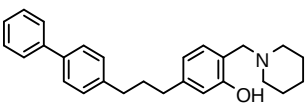
- Molecular mass (MW) smaller than 500
- Calculated octanol/water partition coefficient (*C*Log*P*) smaller than 5
- Number of hydrogen bond donors (HBD) smaller than 5
- Number of hydrogen bond acceptors (HBA) smaller than 10

Since their publication[117] in 1997, these rules have been extensively tested and discussed. Modifications include the so called rule of 3 (molecular mass<300, *C*Log*P*<3 and HBA and HBD<3). The rule of 3 selects molecules that can be further modified without exceeding the rule of 5. Additional parameters that have subsequently become important include polar surface area (PSA) that should not exceed 60. PSA is formed by polar atoms of a molecule and is a descriptor that shows good correlation with passive molecular membrane transport and so allows estimation of transport properties of drugs. PSA is important for drugs that need to cross the blood-brain barrier.

The most important parameter has proved to be the *C*Log*P* value. Compounds which are too polar (*C*Log*P*>5) suffer from poor bioavailability. *C*Log*P* is cumbersome to determine experimentally but can fortunately be calculated fairly accurately and is thus a good example of a QSAR application. Table 2.14 gives the *C*Log*P*, HBD, HBA, MW and PSA values of our most promising compounds.

Table 2.14: Lipinski's rule of 5 parameters of our most promising compounds.

Compound	**Structure**	***C*Log*P***	**HBD**	**HBA**	**MW (g/mol)**	**PSA**
64		5.346	1	3	339.479	32.700
67		5.570	1	2	327.443	23.466
69		6.455	1	2	337.507	23.466

Compound	Structure	*C*Log*P*	HBD	HBA	MW (g/mol)	PSA
66		6.310	1	2	377.450	23.466
41		4.154	1	4	351.183	49.771
53		4.153	1	3	339.164	40.537
61		3.765	1	3	329.145	40.537
65		6.323	1	4	436.309	35.938
70		5.073	1	2	315.166	23.466
77		4.868	1	2	295.426	23.466
89		4.898	1	2	295.194	23.466
90		7.315	1	2	385.241	23.466

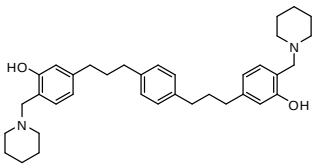
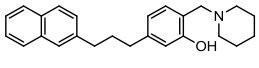
Compound	Structure	*C*Log*P*	HBD	HBA	MW (g/mol)	PSA
93		8.712	2	4	540.372	46.932
95		6.601	1	2	359.225	23.466

Table 2.14 indicates that calculated properties of our compounds mostly do not violate the Lipinski rules and will thus have acceptable bioavailability. The low PSA values indicate good penetration of the blood-brain barrier.

2.13 Structure elucidation

The following salient features can be seen in the NMR spectra of our aminoalkylated chalcones and analogues:

i) Aminoalkylated chalcones –^{1}H NMR and ^{13}C NMR

a) The expected aromatic A-ring resonances between 8.5 and 7.0 ppm. These are often AA'BB' systems with J = 8.9 Hz (H-2', H-6' and H-3', H-5').
b) Most of our compounds have an ABX system on the aromatic B-ring between 7.5 and 6.5 ppm with J = 1.5 and 7.5 Hz (H-2", H-5" and H-6").
c) The chalcones are always the *trans*-isomer between 8.0 and 7.5 ppm with J = 15.6 Hz.
d) The two aminoalkyl methylene protons between the aromatic ring and the N-group are represented by a singlet, resonating at around 3.74 ppm which integrates for two protons. They are often accompanied by the methylene protons *ortho* to the nitrogen of the heterocyclic amine ring e.g. H-2 and H-6 of piperidine which resonates as a four proton broadend singlet.

e) The protons on the amine-moiety which are not *ortho* resonates between 2.50–1.50 ppm mostly as broadend singlets. These are sometimes br by restricted rotation attributed to hydrogen bonding between the *ortho* hydroxyl group and the amino-group.
f) Carbonyl carbon resonance at around 190 ppm.

ii) Aminoalkylated dihydrochalcones – ^{1}H NMR and ^{13}C NMR

a) The characteristic AA'BB' and ABX systems similar to those of the aminoalkylated chalcones.
b) Two triplets at δ 3.24 and 2.96, which integrates for two protons each representing the reduced double bond protons, H-2 and H-3.
c) Carbonyl resonance at around 192 ppm.

iii) Aminoalkylated diarylpropanes – ^{1}H NMR and ^{13}C NMR

a) The characteristic AA'BB' system similar to that of the aminoalkylated chalcones.
b) The characteristic ABX system on the B-ring between 7.0 and 6.5 ppm with J = 1.5 and 7.5 Hz (H-2", H-5"' and H-6"').
c) Two triplets at δ 2.55 and 2.49, which integrates for two protons each representing the fully reduced propyl moeity, H-1 and H-3.
d) A multiplet at δ 1.89 – 1.80 which integrates for two protons on H-2.
e) Absence of carbonyl resonance in ^{13}C NMR spectra.

iv) Aminoalkylated chalcones, dihydrochalcones and diarylpropanes coupled to F or CF_3 – ^{1}H NMR and ^{13}C NMR

^{19}F (natural abundance 100%) has a spin quantum number I of ½, the same as ^{1}H. The signals of hydrogen or carbon atoms up to a distance of four bonds are split by coupling to ^{19}F into n + 1 parts where n is the number of F atoms. The following salient features can be seen in the ^{1}H NMR and ^{13}C NMR spectra of our aminoalkylated chalcones, dihydrochalcones as well as the diarylpropanes containing a fluorine group in the 4-position on the A-ring:

a) The doublet seen at around 7.97 ppm is further split into a doublet of doublets in the ^{1}H NMR spectra (2H, dd, $^{3}J_{H-H}$ = 8.6 Hz; $^{4}J_{H-F}$ = 5.5 Hz, H-2', H-6').
b) The doublet seen at around 6.87 ppm is seen as a triplet in the ^{1}H NMR spectra (2H, t, $^{3}J_{H-H}$ = 8.6 Hz; $^{4}J_{H-F}$ = 8.6 Hz, H-3', H-5').
c) The first C-F coupling is seen as a doublet at 161.2 ppm with a very large J-coupling where the fluorine is one bond from the specific carbon (1C, d, $^{1}J_{C-F}$ = 243.1 Hz, C-4'). The second, third and fourth C-F couplings are seen at the following positions, 138.0 (1C, d, $^{4}J_{C-F}$ = 3.2 Hz, C-1'), 129.7 (2C, d, $^{3}J_{C-F}$ = 7.7 Hz, C-2', C-6'), 115.0 (2C, d, $^{2}J_{C-F}$ = 20.9 Hz, C-3', C-5') with the fluorine atom being two, three or four bonds from that specific carbon.

The following salient features can be seen in the ^{1}H NMR and ^{13}C NMR spectra of our aminoalkylated chalcones, dihydrochalcones and the diarylpropanes containing a CF_3 group in the 4-position on the A-ring:

a) No additional splitting is observed in the ^{1}H NMR spectra.
b) The first C-F coupling is seen as a quartet at δ 124.4 with a large J-coupling which corresponds to the carbon bonded to F_3 (1C, q, $^{1}J_{C-F}$ = 272.2 Hz, **C**F_3). The rest of the C-F couplings are seen at δ 128.1 (1C, q, $^{2}J_{C-F}$ = 32.3 Hz, C-4') and 125.2 (2C, q, $^{3}J_{C-F}$ = 3.9 Hz, C-3', C-5').

2.14 Conclusion

Apart from the fact that our aminoalkylated diarylpropanes are completely novel and totally unrelated to existing antimalarial drugs with a consequently low probability of resistance, we also understand and control our compounds and can thus make analogues at will. This is further enhanced by the fact that our compounds are relatively small and easy and cheap to manufacture.

The following conclusion may be drawn:

- We have established that chalcones with an aminoalkyl moiety on one of the aromatic rings have promising *in vitro* antimalarial and anticancer (see next section) activity.

- This finding supports our hypothesis that nitrogen containing flavonoids will have enhanced biological activity compared to naturally occurring non nitrogen containing flavonoids.
- We used the Mannich reaction to introduce the aminoalkyl moiety. This reaction requires an aromatic OH in the *ortho* position.
- We synthesised a total of 60 compounds in an effort to enhance bioactivity, reduce toxicity and increase oral bioavailability.
- Some of our compounds have similar IC_{50} values to chloroquine against chloroquine sensitive malaria strains (D10 and NF54 strains)
- There is little difference in activity against chloroquine sensitive and chloroquine resistant strains (Dd2 and K1 strains) as is evident from the small RI values.
- This activity against drug resistant malaria strains is to be expected as our compounds are novel with structures totally unrelated to currently used antimalarial drugs.
- Our antimalarial compounds are relatively uncomplicated and inexpensive to manufacture and promise cheap antimalarial drugs.
- Reduction of the enone moiety (reduction of the chalcone to a diarylpropane) increases bioactivity by almost a hundred fold.
- Toxicity tests (*in vitro* CHO cell assays) suggest that our compounds are relatively non-toxic with high SI indices. This is supported by initial *in vivo* mice tests (Mr Abay's PhD thesis)[137] where mice showed no adverse effects after dosage with selected analogues.
- Initial bioavailability determinations (Mr Abay's thesis)[137] gave poor results (3%).
- Initial efforts to enhance bioavailability *via* protecting the phenolic OH group against first-pass metabolism (prodrug strategy) failed because the *ortho* OH group resisted ether and ester formation. We attribute this to hydrogen bonding of the OH to the *ortho* aminoalkyl group *via* a six membered ring.
- Further investigations indicate that bulky groups on the A-ring increase bioavailability.
- Our best candidate with large moieties on the A-ring thus far has a bioavailability of 25%. This is already within a commercially acceptable range as some commercial drugs have similar values.
- It is uncertain whether the bulky group increase bioavailability *via* steric protection of the B-ring OH group against first-pass metabolism or *via* increased liphophilicity

(*C*Log*P*).

- Bioavailability may also be increased *via* formulation if other efforts fail.
- Rudimentary QSAR calculations suggest that our compounds conform to the Lipinski rules (*C*Log*P*<5, PSA<60 etc.).
- Further work is in progress to establish whether the OH group (*ortho* to the aminoalkyl group) is necessary for antimalarial activity. We strive to enhance bioavailability *via* bulky groups on the A-ring, derivatization of the aromatic OH group (prodrug strategy) and formulation, including microformulation. Our compounds were tested in anticancer screens (see next section) and tuberculosis screens will be done in the near future.

2.15 Cancer screening

As discussed in the literature review, a correlation is sometimes observed between anticancer and antimalarial properties of compounds. We thus submitted our nitrogen containing chalcones and analogues for anticancer screening to the CSIR for testing according to The National Cancer Institute (NCI) protocols.

The National Cancer Institute (NCI) in the USA is a nonprofit organization that aims to identify compounds from natural products and other sources with anti-cancer growth inhibitory effects. They use a standard array of 64 cancer cell lines to test growth inhibitory effects with the Sulforhodamine B assay (see page 95–98 for the complete assay information). Three representative cell lines from this array, TK10 (renal), UACC62 (melanoma) and MCF7 (breast) are routinely used by the CSIR.

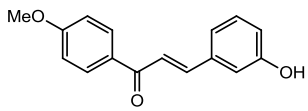
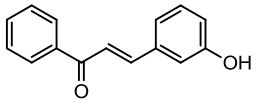
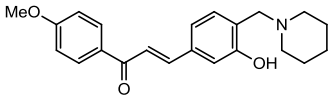
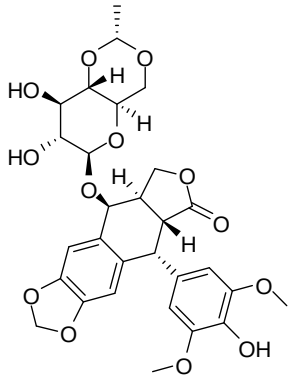
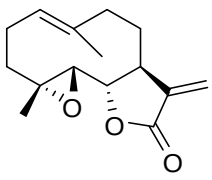
The results are summarized in Tables 2.15–2.23. We used the same sequence that we use to report our antimalarial results to highlight the effect of structural modifications on bioactivity. In contrast with the antimalarial results, where data was reported as IC_{50} values, to emphasize the killing of malaria organisms, the anticancer results are given in TGI (drug concentration resulting in total growth inhibition) values, to reflect that the cancer cells are not killed but prevented from proliferating. The complete data is given in Appendix B, where GI_{50} (50% growth inhibition), LC_{50} (50% lethal concentration) and LC_{100} (100% lethal concentration) values are also given. Parthenolide and etoposide, well-known anticancer agents, were used as reference standards. The results are presented as follows:

- Anticancer bioactivity of our initial chalcones and aminoalkylated chalcones (Table 2.15).
- Anticancer bioactivity of aminoalkylated chalcones with different B-ring substituents (Table 2.16).
- Anticancer bioactivity of aminoalkylated chalcones with different A-ring substituents (Table 2.17).
- Anticancer bioactivity of the dihydrochalcone analogues (Table 2.18).
- Anticancer bioactivity of the diarylpropane analogues with parthenolide as standard

(Table 2.19).

- Anticancer bioactivity of the hydrochloric acid salt of some of the diarylpropanes (Table 2.20).
- Anticancer bioactivity results on structural modifications to compound **41** (Table 2.21).
- Anticancer bioactivity of the analogues with modified chain lengths (Table 2.22).
- Anticancer bioactivity of other chalcone analogues (Table 2.23).

Table 2.15: Anticancer bioactivity of our initial chalcones and aminoalkylated chalcones against all three cell lines.

Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
39	OslbAnke1		25.98	6.02	13.21
40	Ojvdwaw737		13.18	7.04	8.79
41	Ojvdwaw720		20.26	5.52	5.83
	Etoposide		65.48	74.06	>100
	Parthenolide		4.82	4.47	4.02

According to the CSIR's criteria, compounds are considered inactive if parameter TGI for two cell lines is higher than 50 µg/mL or 100 µM.

Table 2.16: Anticancer bioactivity of aminoalkylated chalcones with different B-ring substituents.

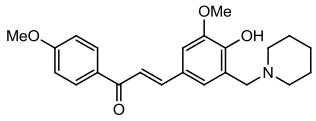
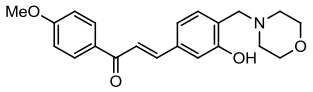
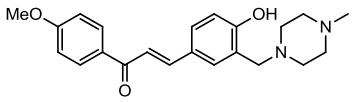
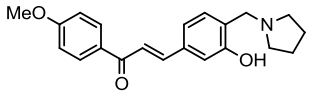
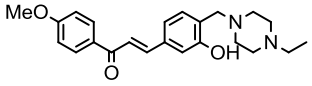
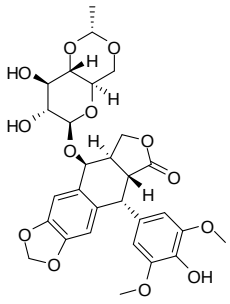
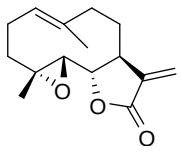
Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
43	Ojvdwaw722		58.96	46.83	48.31
44	Ojvdwaw723		17.48	6.60	21.06
45	OslbAnke4		34.92	6.04	16.74
46	Ojvdwaw743		9.04	6.63	5.79
47	Ojvdwaw744		14.59	8.43	6.74
	Etoposide		44.35	33.87	>100
	Parthenolide		4.82	4.47	4.02

Table 2.17: Anticancer bioactivity of aminoalkylated chalcones with different A-ring substituents.

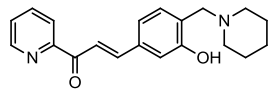
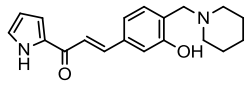
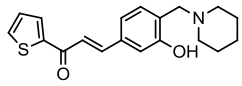
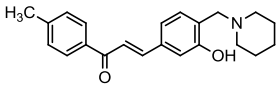
Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
54	NP-059		5.68	4.93	4.49
55	NP-042		15.55	24.36	16.97
56	NP-044		5.36	4.81	1.99
57	NP-072		5.05	5.05	2.45

Table 2.18: Anticancer bioactivity of the dihydrochalcone analogues.

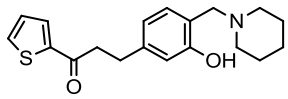
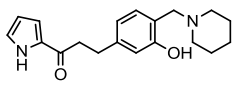
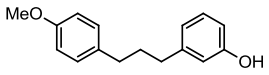
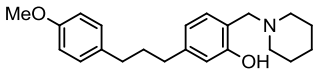
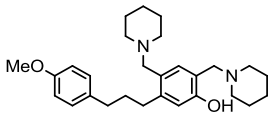
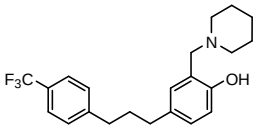
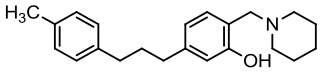
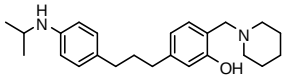
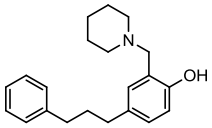
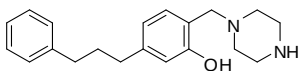
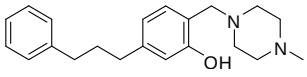
Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
61	NP-054		>100	>100	>100
62	NP-045		70.31	48.09	50.02

Table 2.19: Anticancer bioactivity of the diarylpropane analogues with parthenolide as standard.

Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
63	Ojvdwaw738		>100	>100	83.26
64	Ojvdwaw742		47.72	35.33	51.25
65	Ojvdwaw750		46.05	6.19	44.66
66	NP-102		58.14	56.74	61.66
68	NP-074		30.63	6.84	8.18
71	Pravin.K065		27.07	7.24	11.58
72	NP-0119		41.75	6.42	29.24
74	NP-0106		41.82	7.86	9.27
75	NP-0107		20.91	6.53	9.29

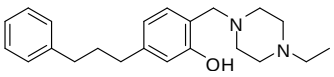
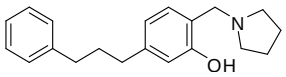
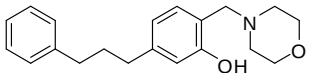
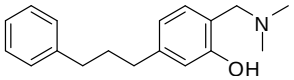
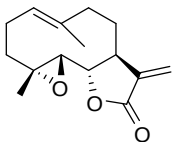
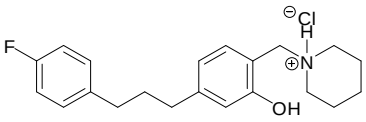
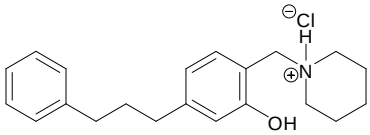
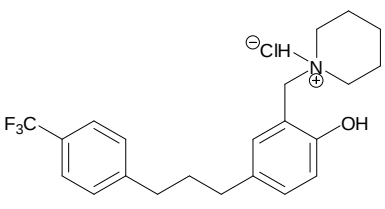
Compound	Code	Structure	TGI,μM TK-10	TGI,μM UACC-62	TGI,μM MCF-7
76	NP-0108		8.06	5.94	7.09
77	NP-0112		41.73	6.37	12.52
78	NP-0113		49.47	49.12	44.16
79	NP-0114		42.88	6.58	23.41
	Parthenolide		4.82	4.47	4.02

Table 2.20: Anticancer bioactivity of the hydrochloric acid salt of some of the diarylpropanes.

Compound	Code	Structure	TGI, μM TK-10	TGI, μM UACC-62	TGI, μM MCF-7
81	NP-046 (salt)		43.28	6.02	14.82
82	NP-036 (salt)		8.20	6.06	18.72
83	NP-102 (salt)		56.73	53.73	52.92

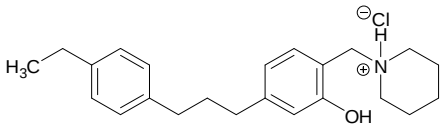
Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
84	NP-085 (salt)		57.21	9.62	54.95

Table 2.21: Anticancer bioactivity results on structural modifications to compound **41**.

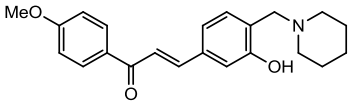
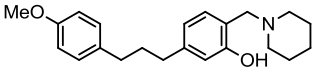
Compound	Code	Structure	TGI, µM TK-10	TGI, µM UACC-62	TGI, µM MCF-7
41	Ojvdwaw720		20.26	5.52	5.83
64	Ojvdwaw742		47.72	35.33	51.25

Table 2.22: Anticancer bioactivity of the analogues with modified chain lengths.

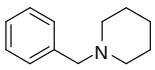
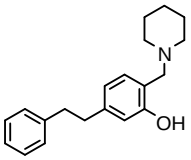
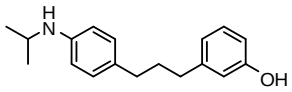
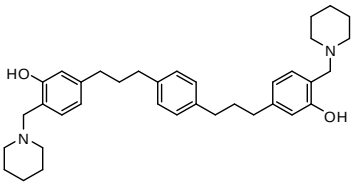
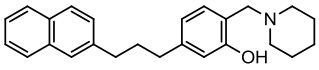
Compound	Code	Structure	TGI,µM TK-10	TGI,µM UACC-62	TGI,µM MCF-7
85	Pravin.K049		>100	84.79	98.45
89	Pravin.K034		40.48	9.88	48.48

Table 2.23: Anticancer bioactivity of other chalcone analogues.

Compound	Code	Structure	TGI,µM TK-10	TGI,µM UACC-62	TGI,µM MCF-7
92	Pravin.K064		37.61	37.42	30.41
93	Pravin.K057		27.78	2.11	5.80
95	NP-0123		49.30	6.27	41.05

The CSIR classifies there results according to table CV:

Table 2.24: Classification of compounds according to the CSIR.

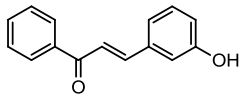
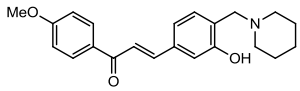
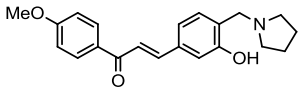
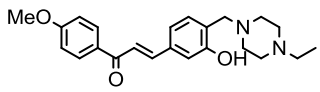
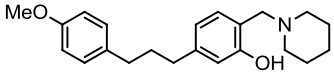
TGI	Status
> 100 µM	Inactive
<100 µM >30 µM	Weak Activity
<30 µM > 10 µM	Moderate Activity
< 10 µM	Potent Activity

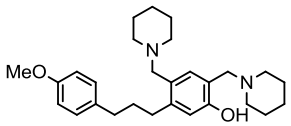
From the tables we can conclude that some of our compounds have potent anti-cancer properties. We already know from our CHO *in vitro* results (Table 2.13) that our compounds are relatively nontoxic, and we know that we probably can increase our bioavailability to a high level. Oral bioavailability and toxicity is less important in cancer since cancer patients are prepared to accept daily injections and unpleasant side effects. Our potent compounds are

given in red in Table 2.15–2.20. Of further interest is the observation that TGI values from the same compounds often differ between TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cell lines. These suggest selectivity and a window of opportunity in terms of a dose that will kill cancer cells and not normal healthy cells.

The CSIR has a HeLa toxicity screen. Due to capacity constraints only a few of our compounds were tested in this essay. The toxicity was also expressed in TGI values and is thus not totally comparable with our CHO values (IC_{50}). The results are given in Table 2.25.

Table 2.25: Toxicity and SI values using HeLa cell lines of some of our aminoalkylated chalcones

Compound	Structure	TGI,µM TK-10	TGI,µM UACC-62	TGI,µM MCF-7	HeLa toxicity TGI, µM
40		13.18	7.04	8.79	48.30
41		20.26	5.52	5.83	27.02
46		9.04	6.63	5.79	18.11
47		14.59	8.43	6.74	27.73
64		47.72	35.33	51.25	56.63

65		46.05	6.19	44.66	56.83

The HeLa values also indicate that our compounds are relatively nontoxic. HeLa cells are derived from cancer cells and are not considered good indicators of toxicity of anticancer compounds.

2.16 Conclusion

- In contrast with antimalarial activity, aminoalkylation of chalcones do not lead to a dramatic inhibition of cancer growth. Normal non-nitrogen containing chalcones show significant anticancer activity.
- Aminoalkylation of chalcones does not reduce anticancer properties.
- Removal of the double bond of aminoalkylated chalcones however leads to a significant reduction in anticancer bioactivity and aminoalkylated dihydrochalcones are much less reactive than their corresponding aminoalkylated chalcone analogues.
- We thus believe that the enone moiety is involved in anticancer activity.
- Aminoalkylation of the diarylpropanes (fully reduced chalcones without an enone moiety) however leads to recovery of anticancer properties. This suggests that an alternative mode of action, not associated with the enone moiety, but with the aminoalkyl moiety, operates.
- This finding is not trivial, since normal chalcones are known to be toxic and demonstrate low or zero bioavailability. Our aminoalkylated diarylpropanes, in contrast have mostly low toxicity and promising bioavailability (see previous section).
- Our compounds are generally least active against TK-10 (renal), modestly active against MCF-7 and most active against UACC-62 (melanoma) cancer cell lines. This is significant since few commercial drugs are available to treat melanoma.
- Our most promising candidate so far (compound **93**) has a TGI of 2.11, smaller than parthenolide (4.47) in the UACC-62 *in vitro* assay.

3 Standard Experimental Techniques & bioassay procedures

The following general techniques were used during this study.

3.1 CHROMATOGRAPHIC TECHNIQUES

3.1.1 Thin Layer Chromatography

Qualitative thin layer chromatography (TLC) was conducted on Merck aluminium sheets (silica gel 60 F_{254}, 0.25 mm) divided into strips of ca. 3 x 6 cm. R_f values were reported as those observed in the qualitative TLC assessments. Preparative thin layer chromatography was conducted on glass plates (20 x 20 cm), coated with a layer (1.0 mm) Kieselgel PF_{254} (100 g Kieselgel in 230 ml distilled water per 5 plates). The plates were dried at room temperature and used unactivated. The plates were loaded with a maximum of 25 mg material per plate in about 100 mL of pre-determined development solvent. After development in the appropriate eluent, the plates were dried in a fast stream of air and the bands identified by either UV-light (254 nm) or by the appropriate spraying reagent. The carefully marked out and collected bands were eluted with acetone and the acetone removed under reduced pressure (rotary evaporator) at about 40 °C. Small-scale separations were conducted on Merck Precoated (0.25 mm) TLC Plates Silica Gel 60 F_{254} with each plate charged with 3–5 mg of crude product.

3.1.2 Column Chromatography

Separations on Sephadex LH-20 from Pharmacia and Kieselgel from Merck (Art 773, 170-230 mesh) were performed with various column sizes and at differing flow rates. Fractions were collected in test tubes. Flash column chromatography (FCC) was performed on a glass column (5 cm diameter) charged with 10.0 g of Merck Kieselgel 60 (230–400 mesh) for

every 1 g of the crude product. The crude material was dissolved in a minimum amount of the appropriate solvent and carefully applied to the column with a pasteur pipette. A flow of nitrogen (about 50 kPa pressure) through the appropriate solvent separated the sample into clean fractions. The fractions were collected and the solvent was removed under reduced pressure by rotary evaporation.

3.1.3 Spraying Reagents

Thin-layer chromatograms were sprayed with a 2% (v/v) solution of formaldehyde (40% solution in water) and concentrated sulphuric acid and subsequently heated to 110 ºC to effect maximum development of colour.

3.2 SPECTROSCOPIC METHODS

3.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

A 600 MHz Bruker Avance spectrometer was used to record the ^{1}H NMR, NOE, COSY, HMBC, HMQC (600 MHz) and ^{13}C, APT (150 MHz) experiments. The solvents used were chloroform-*d*$_1$ ($CDCl_3$: δ_H= 7.24; δ_C = 77.2 ppm), acetone-*d*$_6$ (δ_H = 2.04; δ_C = 29.8 ppm) and methanol-*d*$_4$ (MeOD: δ_H = 4.87 and 3.31; δ_C = 49.2 ppm) with TMS (tetramethysilane) as internal standard. Chemical shifts were expressed as parts per million (ppm) on the delta (δ) scale and coupling constants (*J*) are accurate to 0.01 Hz. The following abbreviations were used in describing ^{1}H NMR signal multiplicities:

s	singlet	dd	doublet of doublets
d	doublet	t	triplet
q	quartet	m	multiplet

3.2.2 Mass Spectrometry (MS)

High resolution mass spectra were recorded on a Waters Micromass LCT Premier TOF-MS mass spectrometer. All samples were dissolved and diluted to ~ 2 ng/µL and infused without additives.

3.2.3 Infrared (IR)

Solid state FR-IR spectra were recorded as neat compound on a Bruker Tensor 27 spectrometer in the range of 3000 - 600 cm^{-1}.

3.2.4 Melting points

Melting points were determined with a Reichert Thermopan microscope with a Koffler hot–stage and are uncorrected.

3.2.5 High performance liquid chromatography (HPLC)

Purity was measured using Shimadzu high performance liquid chromatography (HPLC) systems using Phenomenex C18 (100 mm x 4.6 mm) 2.6µ column; 2.0 µL injection volume; flow, 0.2 mL/min; isocratic system, mobile phase A, 0.1% formic acid in H_2O and mobile phase B, acetonitrile with a Shimadzu LC-20AD pump SPD-M20A UV detector set at 254 nm.

3.3 ANHYDROUS SOLVENTS AND REAGENTS

Acetone was left over dry K_2CO_3 (oven-dried, 24 hours, 200 ºC) for 24 hours. The K_2CO_3 was filtered off and the solvent distilled over 3 Å molecular sieves and stored under N_2.

Dichloromethane and dimethylformamide were refluxed over CaH_2 under N_2 for 12 hours with subsequent fresh distillation under N_2 before use.

3.4 FREEZE-DRYING

Phenolic material in aqueous solution was freeze-dried using a Vacutex Freezemobile.

3.5 BIOASSAYS

3.5.1 Antimalarial bioactivity testing performed by UCT

***In vitro* antimalarial activity against D10/NF54 strain**

Objectives

- To test samples for *in vitro* antiplasmodial activity against a chloroquine sensitive (CQS) strain of *Plasmodium falciparum* (D10)
- To test samples for *in vitro* cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT)-assay

Antiplasmodial assay

Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[154] Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler.[155] The test samples were tested in triplicate on one or two separate occasions.

The test samples were prepared to a 20 mg/mL stock solution in 100% DMSO. Stock solutions were stored at -20 ºC. Further dilutions were prepared in DMSO and complete medium on the day of the experiment. Samples were tested as a suspension if not completely

[154] Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673-675.
[155] Makler, M. T.; Ries, J. M.; Williams, J. A.; Bancroft, J. E.; Piper, R. C.; Gibbins, B. L.; Hinrichs, D. J. *The American Society of Tropical Medicine and Hygiene* **1993**, *48*, 739-741.

dissolved. Chloroquine (CQ) was used as the reference drug. A full dose-response was performed to determine the concentration inhibiting 50% of parasite growth (IC_{50}–value). Test samples were initially tested at a starting concentration of 100 µg/mL, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.2 µg/mL. The same dilution technique was used for all samples. Active samples were re-tested at a starting concentration of 10 µg/mL or 1000 ng/mL. CQ was tested at a starting concentration of 100 ng/mL. The highest concentration of solvent (0.5%) to which the parasites were exposed had no measurable effect on the parasite viability (data not shown).

Introduction

Antimalarial activity screening of synthesized compounds is used to determine the potential of these as sources of antimalarial compounds.[156,157] A good source of antimalarial compounds should also inhibit parasites selectively and be harmless towards other cells. Cytotoxicity experiments are used to determine general toxic properties of compounds against living cells. Antimalarial activity and cytotoxicity information are used to determine selectivity indexes, which are used as a guide to determine the potential of a compound for further investigation. Evaluation criteria on this subject varies, but according to a review article by Richard Pink and co-authors,[153] an active antimalarial compound should be at least tenfold more active against the targeted organism than against mammalian cells to be considered for further testing.

Cytotoxicity was tested against Chinese hamster ovarian (CHO) cells which were cultured according to a standard operating procedure prepared by the Pharmacology Department at the University of Cape Town, South Africa. The MTT assay as described by Mosmann (with minor modifications) was used to determine cell viability.[158]

The synthetic compounds were screened against a chloroquine sensitive *P. falciparum* strain (D10), and a chloroquine resistant *P. falciparum* strain (K1). Cytotoxicity screening of these compounds were also performed.

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[156] Clarkson, C.; Campbell, W. E.; Smith, P. J. *PlantaMedica* **2003**, *69*, 720-724.
[157] Clarkson, C.; Maharaj, V. J.; Crouch, N. R.; Grace, O. M.; Pillay, P.; Matsabisa, M. G.; Bhagwandin, N.; Smith, P. J.; Folb, P. I. *South African Journal of Ethnopharmacology* **2004**, *92*, 177-191.
[158] Mosmann, T. *Journal of Immunological Methods* **1983**, *65*, 55-63.

Cytotoxicity assay

The MTT-assay is used as a colorimetric assay for cellular growth and survival, and compares well with other available assays.[159,160] The tetrazolium salt MTT was used to measure all growth and chemosensitivity. The test samples were tested in triplicate on one occasion.

The sample preparation was the same as for the antimalarial testing. Dilutions were prepared on the day of the experiment. Emetine was used as the reference drug in all experiments. The initial concentration of emetine was 100 µg/mL, which was serially diluted in complete medium with 10-fold dilutions to give 6 concentrations, the lowest being 0.001 µg/mL. The same dilution technique was applied to all the test samples. The highest concentration of solvent (0.5%) to which the cells were exposed to had no measurable effect on the cell viability (data not shown).

The 50% inhibitory concentration (IC_{50}) values were obtained from full dose-response curves, using a non-linear dose-response curve fitting analysis via GraphPad Prism v.4 software. The CHO test was performed by Ntokozo Dambuza at UCT.

3.5.2 Anticancer bioactivity testing

Assay Background

The growth inhibitory effects of the compounds were tested in the 3-cell line panel consisting of TK10 (renal), UACC62 (melanoma) and MCF7 (breast) by Sulforhodamine B (SRB) assay. The SRB assay was developed by Skehan and colleagues[161] to measure drug-induced cytotoxicity and cell proliferation. Its principle is based on the ability of the protein dye sulforhodamine B (Acid Red 52) to bind electrostatically in a pH-dependent manner to protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mild acidic conditions it binds to the fixed cellular protein, while under mild basic conditions it can be

[159]Mosmann, T. *Journal of Immunological Methods* **1983**, *65*, 55-63.
[160]Rubinstein, L. V.; Shoemaker, R. H.; Paull, K. D.; Simon, R. M.; Tosini, S.; Skehan, P.; Scudiero, D. A.; Monks, A.; Boyd, M. R. *Journal of the National Cancer Institute* **1990**, *82*, 1113-1118.
[161]Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107-1112.

extracted from cells and solubilized for measurement. The SRB Assay is performed at CSIR in accordance with the protocol of the Drug Evaluation Branch, NCI, and the assay has been adopted for this screen. Natasha Kolesnikova from the CSIR conducted all the anticancer experiments.

Materials and method

The human cell lines TK10, UACC62 and MCF7 was obtained from NCI in the framework of a collaborative research program between CSIR and NCI. Cell lines were routinely maintained as a monolayer cell culture at 37 ºC, 5% CO_2, 95% air and 100% relative humidity in RPMI containing 5% fetal bovine serum, 2 mM L-glutamine and 50 µg/mL gentamicin.

For screening experiment, the cells (3–19 passages) were inoculated in a 96-well microtiter plates at plating densities of 7–10 000 cells/well and were incubated for 24 h. After 24 h one plate was fixed with TCA to represent a measurement of the cell population for each cell line at the time of drug addition (T_0). The other plates with cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations (6.25–100 ppm). Cells without drug addition served as control. The blank contains complete medium without cells. Etoposide was used as a standard.

The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10 mM Tris base for optical density determination at the wavelength 540 nm using a multiwell spectrophotometer. The optical density of the test well after 48 h period of exposure to test drug is T_i, the optical density at time zero is T_0, and the control optical density is C. Percentage cell growth is calculated as:

$$[(Ti-T_0)/(C-T_0)] \times 100 \text{ for concentrations at which } Ti \geq T_0$$

$$[(Ti-T_0)/T_0] \times 100 \text{ for concentrations at which } Ti < T_0.$$

The TGI is the concentration of test drug where $100 \times (T_i-T_0)/(C-T_0) = 0$. The TGI signifies a cytostatic effect.

The results of five dose screening were reported as TGI (total growth inhibition). The biological activities were separated into 4 categories: inactive (TGI>50 µg/mL or TGI >100 µM), weak activity (15 µg/mL<TGI<50 µg/mL or 30 µM<TGI<100 µM), moderate activity (6.25 µg/mL<TGI<15 µg/mL or 10 µM<TGI<30 µM) and potent activity (TGI<6.25 µg/mL or TGI<10 µM).

For each tested compound, four response parameters, GI_{50} (50% growth inhibition and signifies the growth inhibitory power of the test agent), TGI (which is the drug concentration resulting in total growth inhibition and signifies the cytostatic effect of the test agent), LC_{50} (50% lethal concentration and signifies the cytotoxic effect of the test agent), LC_{100} (100% lethal concentration and signifies the cytotoxic effect of the test agent), were calculated for each cellline.

Cytotoxicity assay

Assay Background

The cytotoxic effects of the compounds were tested by Sulforhodamine B (SRB) assay on the HeLa cell line. The SRB assay was developed by Skehan and colleagues to measure drug-induced cytotoxicity and cell proliferation. Its principle is based on the ability of the protein dye sulforhodamine B (Acid Red 52) to bind electrostatically in a pH-dependent manner to protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mild acidic conditions it binds to the fixed cellular protein, while under mild basic conditions it can be extracted from cells and solubilized for measurement. The SRB Assay is performed at CSIR in accordance with the protocol of the Drug Evaluation Branch, NCI, and the assay has been adopted for this screen.

Materials and method

The HeLa cell line (Human Negroid cervix epitheloid adenocarcinoma, ECACC) was routinely maintained as a monolayer cell culture at 37 ºC, 5% CO_2, 95% air and 100% relative humidity in EMEM containing 5% fetal bovine serum, 2 mM L-glutamine and 50µg/mL gentamicin.

For screening experiment, the cells (3-19 passages) were inoculated in a 96-well microtiter plates at plating densities of 7 000 cells/well and were incubated for 24 h. After 24 h one plate was fixed with TCA to represent a measurement of the cell population at the time of drug addition (T_0). The other plates with cells were treated with the experimental drugs which were previously dissolvedin DMSO and diluted in medium to produce 5 concentrations (6.25-100 µg/mL or 0.01-100µM). Cells without drug addition served as control. The blank contains complete medium without cells. Emetine was used as a reference standard.

The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10mM Tris base for optical density determination at the wavelength 540 nm using a multiwell spectrophotometer. Optical density measurements were used to calculate the net percentage cell growth. The optical density of the test well after 48-h period of exposure to test drug is Ti, the optical density at time zero is T_0, and the control optical density is C. Percentage cell growth is calculated as:

$[(Ti-T_0)/(C-T_0)] \times 100$ for concentrations at which $Ti \geq T_0$

$[(Ti-T_0)/T_0] \times 100$ for concentrations at which $Ti < T_0$.

The results of five dose screening were reported as TGI (total growth inhibition). The TGI is the concentration of test drug where $100 \times (T-T_0)/(C-T_0) = 0$. The TGI signifies a cytostatic effect. For each tested compound, four response parameters, GI_{50} (50% growth inhibition and signifies the growth inhibitory power of the test agent), TGI (which is the drug concentration resulting in total growth inhibition and signifies the cytostatic effect of the test agent), LC_{50} (50% lethal concentration and signifies the cytotoxic effect of the test agent), LC_{100} (100% lethal concentration and signifies the cytotoxic effect of the test agent), were calculated.

4 Experimental procedures

Please take note of the following:

All chemical structures were named according to IUPAC rules. The numbering was modified on the NMR plates to simplify the structure elucidation.

The syntheses and NMR plates of all our compounds are given in this section. Not all intermediate compounds were tested for bioactivity and do not appear in Chapter 2. Complete detail of their synthesis and characterization is given to justify our final compounds.

General procedure for the synthesis of chalcones (1,3-diaryl-2-propenones) *via* the Aldol condensation

A mixture of acetophenone (1 eq.) and aryl aldehyde (1 eq.) was stirred in EtOH (50 mL) at room temperature. KOH solution (50%, 25 mL) was added after 10 minutes, which turned the reaction mixture bright yellow. The reaction mixture was left to stir overnight, after which it was quenched with ice-cold 1 N HCl (100 mL) solution and extracted with EtOAc (2 x 50 mL). The organic layer was washed with water (1 x 50 mL), dried over Na_2SO_4, and the solvent evaporated under reduced pressure.

1. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (39)

Compound (**39**) was synthesized according to the general procedure using 4-methoxyacetophenone (3.1356 g; 20.9 mmol) and 3-hydroxybenzaldehyde (3.0547 g; 25.0 mmol) as starting materials.

Recrystallization from EtOH yielded the title compound as light yellow crystals[162] (R_f = 0.37, T:A 5:5, 3.506 g, 66%), mp 163-164 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.16 (2H,

[162]Park, E.; Yang, Y. J.; Kwak, J. H.; Jung, Y. H.; Kang, S. C.; Kim, I. S. *Bioorg. & Med. Chem. Lett.* **2012**, *22*, 3653-3655.

d, J = 8.9 Hz, H-2', H-6'), 7.80 (1H, d, J = 15.6 Hz, H-3), 7.69 (1H, d, J = 15.6 Hz, H-2), 7.30 – 7.25 and 6.95 – 6.93 (4H, H-5", H-2", H-6", H-4"), 7.07 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.91 (3H, s, OC**H**$_3$) (Plate 1a). ^{13}C NMR δ (150 MHz, Acetone-d$_6$, Me$_4$Si) 187.4 (C-1), 163.6 (C-4'), 157.8 (C-3"), 143.3 (C-3), 136.7 (C-1"), 131.1 (C-1'), 130.7 (C-2', C-6'), 129.9 (C-5"), 121.9 (C-2), 120.0 (C-6"), 117.4 (C-2"), 114.9 (C-4"), 113.9 (C-3', C-5'), 55.1 (O**C**H$_3$) (Plate 1b).

IR (neat): ν_{max} = 3323.24, 1583.50, 1168.39, 830.84, 666.33 cm^{-1}
Found (ES) [M + H]$^+$ 255.1965, (C$_{16}$H$_{14}$O$_3$ + H$^+$) requires *m/z* 255.1960.

2. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one (40)

Compound (**40**) was synthesized according to the general procedure using acetophenone (2.974 g; 24.7 mmol) and 3-hydroxybenzaldehyde (2.963 g; 24.3 mmol) as starting materials.

Recrystallization from EtOH yielded the title compound as beige crystals[163] (R_f = 0.33, T:A 5:5, 1.260 g, 23%), mp 162-163 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d$_6$, Me$_4$Si) 8.60 (s, 1 x O**H**), 8.17 – 8.13 (2H, m, H-2', H-6'), 7.81 (1H, d, J = 15.6 Hz, H-3), 7.73 (1H, d, J = 15.6 Hz, H-2), 7.66 (1H, tt, J = 6.9, 1.2 Hz, H-4'), 7.60 – 7.55 (2H, m, H-3', H-5'), 7.33 (1H, dt, J = 7.6, 1.2 Hz, H-6"), 7.31 (1H, d, J = 7.6 Hz, H-5"), 7.29 (1H, t, J = 1.9 Hz, H-2"), 6.96 (1H, ddd, J = 7.6, 2.4, 1.3 Hz, H-4") (Plate 2a). ^{13}C NMR δ (150 MHz, Acetone-d$_6$, Me$_4$Si) 189.1 (C-1), 157.8 (C-3"), 144.1 (C-2), 138.2 (C-1'), 136.5 (C-1"), 132.8 (C-4'), 130.0 (C-5"), 128.7 (C-3', C-5'), 128.4 (C-2', C-6'), 122.0 (C-3), 120.1 (C-6"), 117.6 (C-4"), 115.0 (C-2") (Plate 2b).

IR (neat): ν_{max} = 3347.25, 1586.36, 1572.07, 777.78, 699.32 cm^{-1}
Found (ES) [M+H]$^+$ 225.0837, (C$_{15}$H$_{12}$O$_2$ + H$^+$) requires *m/z* 225.0839.

[163]Karki, R.; Kang, Y.; Kim, C. H.; Kwak, K.; Kim, J-A.; Lee, E-S. *Bull. Korean Chem. Soc.* **2012**, *33*, 2925-2929.

3. Synthesis of (*E*)-3-(4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (101)

Compound (**101**) was synthesized according to the general procedure using 4-methoxyacetophenone (3.479 g; 23.2 mmol) and 4-hydroxybenzaldehyde (3.006 g; 24.6 mmol) as starting materials. The chalcone was isolated by column chromatography (cyclohexane:EtOAc 5:5, 3 cm x 30 cm).

The fraction R_f 0.55 yielded 4-hydroxybenzaldehyde as unreacted starting material (1.256 g, 44%). The fraction R_f 0.60 yielded (*E*)-3-(4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**101**) as bright yellow crystals[164] (1.348 g, 23%), mp 148-149 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.14 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.5 Hz, H-3), 7.70 (2H, d, J = 8.6 Hz, H-2'', H-6''), 7.69 (1H, d, J = 15.5 Hz, H-2), 7.06 (2H, d, J = 8.8 Hz, H-3', H-5'), 6.92 (2H, d, J = 8.6 Hz, H-3'', H-5''), 3.91 (3H, s, OC**H$_3$**) (Plate 3a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 187.2 (C-1), 163.4 (C-4'), 159.8 (C-4''), 143.4 (C-3), 131.4 (C-1'), 130.5 (C-2'', C-6''), 130.5 (C-2', C-6'), 126.9 (C-1''), 118.7 (C-2), 115.8 (C-3'', C-5''), 113.7 (C-3', C-5'), 55.0 (O**C**H$_3$) (Plate 3b).

IR (KBr): ν_{max} = 2160.05, 1975.31, 1513.57, 1168.68 cm^{-1}
Found (EI) M^+ 254.0934, $C_{16}H_{14}O_3$ requires 254.0933.

4. Synthesis of (*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (102)

Compound (**102**) was synthesized according to the standard procedure using 4-methoxyacetophenone (3.1628 g; 21.0 mmol) and vanillin (3.8452 g; 25.3 mmol) as starting materials. The chalcone was isolated by column chromatography (T:A 5:5, 3 cm x 30 cm).

The fraction R_f 0.51 yielded vanillin as unreacted starting material (0.789 g, 25%). The fraction R_f 0.56 yielded (*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**102**) as yellow crystals[165] (1.821 g, 29%), mp 161-162 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.13 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.6 Hz, H-3), 7.71 (1H, d, J = 15.6 Hz, H-2), 7.49 (1H, d, J = 2.0 Hz, H-3''), 7.30 (1H, dd, J = 2.0, 8.2 Hz, H-2''),

[164]Wu, J.; Li, J.; Cai, Y.; Pan, Y.; Ye, F.; Zhang, Y.; Zhao, Y.; Yang, S.; Li, X.; Liang, G. *J. Med. Chem.* **2011**, *54(23)*, 8110-8123.
[165]Choudhary, A. N.; Kumar, A.; Juyal, V. *Letters in Drug Design & Discovery* **2012**, *9(5)*, 479-488.

7.06 (2H, d, J = 8.9 Hz, H-3', H-5'), 6.90 (1H, d, J = 8.2 Hz, H-6''), 3.94 (3H, s, OC**H$_3$**), 3.91 (3H, s, OC**H$_3$**) (Plate 4a). ^{13}C NMR δ (150 MHz, Acetone-d$_6$, Me$_4$Si) 188.1 (C-1), 164.3 (C-4'), 150.2 (C-5''), 148.9 (C-4''), 144.7 (C-3), 132.4 (C-1'), 131.4 (C-2', C-6'), 128.3 (C-1''), 124.4 (C-2''), 119.9 (C-2), 116.2 (C-3''), 114.6 (C-3', C-5'), 111.9 (C-6''), 56.4 (O**C**H$_3$), 55.9 (O**C**H$_3$) (Plate 4b).

IR (KBr): ν_{max} = 3369.81, 1650.74, 1602.30, 1567.21, 1511.21 cm^{-1}
Found (EI) M$^+$ 284.1049, $C_{17}H_{16}O_4$ requires 284.1054.

5. Synthesis of (*E*)-1-(4-fluorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (103)

Compound (**103**) was synthesized according to the general procedure using 4-fluoroacetophenone (1.000 g; 7.2 mmol) and 3-hydroxybenzaldehyde (0.883 g; 7.2 mmol) as starting materials. The chalcone was isolated by column chromatography (T:A 5:5, 3 cm x 30 cm).

The fraction R$_f$ 0.52 yielded (*E*)-1-(4-fluorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**103**) as a yellow solid[166] (1.56 g, 90%). ^{1}H NMR δ (600 MHz, CDCl$_3$, Me$_4$Si) 8.04 (2H, dd, $^3J_{H-H}$ = 8.8 Hz; $^4J_{H-F}$ = 5.4 Hz, H-2', H-6'), 7.75 (1H, d, J = 15.6 Hz, H-3), 7.46 (1H, d, J = 15.6 Hz, H-2), 7.28 (1H, t, J = 7.8 Hz, H-5''), 7.20 (1H, d, J = 7.7 Hz, H-4''), 7.16 (2H, t, $^3J_{H-H}$ = 8.8 Hz; $^4J_{H-F}$ = 8.8 Hz, H-3', H-5'), 7.14 – 7.12 (1H, m, H-2''), 6.92 – 6.89 (1H, m, H-6'') (Plate 5a). ^{13}C NMR δ (150 MHz, CDCl$_3$, Me$_4$Si) 189.1 (C-1), 165.7 (1C, d, $^1J_{CF}$ = 255.1 Hz, C-4'), 156.2 (C-3''), 144.9 (C-3), 136.4 (C-1''), 134.4 (1C, d, $^4J_{CF}$ = 2.5 Hz, C-1'), 131.2 (2C, d, $^3J_{CF}$ = 9.2 Hz, C-2', C-6'), 130.3 (C-5''), 121.9 (C-2), 121.2 (C-6''), 117.9 (C-2''), 115.9 (2C, d, $^2J_{CF}$ = 21.8 Hz, C-3', C-5'), 115.0 (C-4'') (Plate 5b and 5c).

IR (neat): ν_{max} = 1577.77, 1507.52, 857.59, 811.33, 572.79 cm^{-1}

6. Synthesis of (*E*)-1-(4-bromophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (104)

Compound (**104**) was synthesized according to the general procedure using 4-bromoacetophenone (1.000 g; 5.0 mmol) and 3-hydroxybenzaldehyde (0.683 g; 5.6 mmol) as

[166]Van Der Westhuizen, J. H.; Eljaleel, A. E. M.; Bonnet, S. L.; Wilhelm-Mouton, A. *PCT Int. Appl*. 2011, WO 2011151789 A2 20111208.

starting materials. The product was separated by column chromatography (T:A 5:5, 3 cm x 30 cm).

The fraction R_f 0.50 yielded (*E*)-1-(4-bromophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one as a light yellow solid[167] (0.960 g, 64%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.81 (2H, d, J = 8.4 Hz, H-2', H-6'), 7.70 (1H, d, J = 15.6 Hz, H-3), 7.58 (2H, d, J = 8.4 Hz, H-3', H-5'), 7.38 (1H, d, J = 15.6 Hz, H-2), 7.23 (1H, t, J = 7.8 Hz, H-5"), 7.15 (1H, d, J = 7.6 Hz, H-6"), 7.09 (1H, br s, H-2"), 6.86 (1H, m, H-4") (Plate 6a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.7 (C-1), 156.1 (C-3"), 145.3 (C-3), 136.8 (C-1'), 136.2 (C-1"), 132.0 (C-3', C-5'), 130.3 (C-5"), 130.1 (C-2', C-6'), 128.1 (C-4'), 121.8 (C-2), 121.2 (C-6"), 118.0 (C-2"), 115.0 (C-4") (Plate 6b).

Found (TOF MS ES) 324.9840, ($C_{15}H_{11}BrO_2$ + Na) requires *m/z* 324.9840.

7. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-*p*-tolylprop-2-en-1-one (105)

Compound (**105**) was synthesized according to the general procedure using 4-methylacetophenone (1.000 g; 7.5 mmol) and 3-hydroxybenzaldehyde (1.000 g; 8.2 mmol) as starting materials. The chalcone was was isolated by column chromatography (H:A 6:4, 3 cm x 30 cm).

The fraction R_f 0.50 yielded (*E*)-3-(3-hydroxyphenyl)-1-*p*-tolylprop-2-en-1-one as a light yellow solid[168] (1.58 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.86 (2H, d, J = 8.2 Hz, H-2', H-6'), 7.69 (1H, d, J = 15.7 Hz, H-3), 7.43 (1H, d, J = 15.7 Hz, H-2), 7.24 – 7.20 (3H, m, H-3', H-5', H-4"), 7.13 (1H, d, J = 7.7 Hz, H-5"), 7.11 (1H, d, J = 2.1 Hz, H-2"), 6.86 (1H, dd, J = 7.7, 2.1 Hz, H-6"), 2.63 (3H, s, C**H$_3$**) (Plate 7a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 190.8 (C-1), 156.4 (C-3"), 144.9(C-3), 144.1 (C-4'), 136.4 (C-1'), 135.4 (C-1"), 130.2 (C-5"), 129.5 (C-2', C-6'), 128.8 (C-3', C-5'), 122.2 (C-2), 120.9 (C-6"), 117.9 (C-2"), 115.2 (C-4"), 21.7 (**C**H_3) (Plate 7b).

[167]Moorthi, S. S.; Chinnakali, K.; Nanjundan, S.; Unnithan, C. S.; Fun, H. K.; Xiao, L. *Acta E.* **2005**, *61(2)*, o483-o485.
[168]Iwata, S.; Nishino, T.; Inoue, H.; Nagata, N.; Satomi, Y.; Nishino, H.; Shibata, S. *Biological & Pharmaceutical Bulletin* **1997**, *20(12)*, 1266-127.

8. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (106)

Compound (**106**) was synthesized according to the general procedure using 2-acetylthiophene (0.2 g; 1.6 mmol) and 3-hydroxybenzaldehyde (0.190 g; 1.6 mmol) as starting materials. The product was separated by column chromatography (H:A 5:5, 1.5 cm x 20 cm).

The fraction R_f 0.50 yielded (*E*)-3-(3-hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one as a light yellow solid[169] (0.329 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.81 (1H, d, J = 3.8 Hz, H-4'), 7.75 (1H, d, J = 15.5 Hz, H-3), 7.63 (1H, d, J = 4.9 Hz, H-2'), 7.34 (1H, d, J = 15.5 Hz, H-2), 7.23 – 6.86 (5H, H-2", H-3', H-4", H-5", H-6") (Plate 8a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 182.3 (C-1), 156.3 (C-3"), 145.3 (C-3), 144.1 (C-1'), 136.2 (C-1"), 134.3 (C-4'), 132.2 (C-5"), 130.2 (C-2'), 128.4 (C-3'), 121.9 (C-2), 121.1 (C-6"), 117.9 (C-2"), 115.1 (C-4") (Plate 8b).

Found (TOF MS ES) $[M-H]^+$ 229.0324, ($C_{13}H_{10}SO_2$ - H^+) requires *m/z* 229.0323.

9. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (107)

Compound (**107**) was synthesized according to the general procedure using 2-acetylpyrrole (0.200 g; 1.8 mmol) and 3-hydroxybenzaldehyde (0.249 g; 2.0 mmol) as starting materials. The product was separated by column chromatography (T:A 6:4, 1.5 cm x 20 cm).

The fraction R_f 0.49 yielded (*E*)-3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one as a light yellow solid (0.300 g, 78%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.70 (1H, d, J = 15.7 Hz, H-3), 7.25 (1H, d, J = 15.7 Hz, H-2), 7.22 (1H, t, J = 7.9 Hz, H-5"), 7.15 (1H, d, J = 7.7 Hz, H-2'), 7.07 – 7.05 (1H, m, H-4"), 7.05 – 7.03 (1H, m, H-6"), 7.02 – 6.99 (1H, m, H-2"), 6.82 (1H, dd, J = 8.0, 3.2 Hz, H-4'), 6.31 – 6.27 (1H, m, H-3') (Plate 9a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 178.8 (C-1), 156.0 (C-3"), 142.0 (C-3), 136.6 (C-1"), 133.1 (C-1'), 130.1 (C-5"), 125.3 (C-4'), 122.3 (C-2'), 121.1 (C-2), 117.4 (C-6"), 116.4 (C-2"), 114.8 (C-4"), 111.2 (C-3') (Plate 9b).

Found (TOF MS ES) $[M-H]^+$ 212.0709, ($C_{13}H_{11}NO_2$ - H^+) requires *m/z* 212.0712.

[169]Tran, T-D.; Nguyen, T-N.; Do, T-H.; Thai, K-M.; Tran, C-D. *International Electronic Conference on Synthetic Organic Chemistry* 2011, a61/1-a61/5.

10. Synthesis of (*E*)-3-(3-hydroxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (108)

Compound (**108**) was synthesized according to the general procedure using 2-acetylpyridine (0.200 mg; 1.7 mmol) and 3-hydroxybenzaldehyde (0.201 g; 1.6 mmol) as starting materials. The product was separated by column chromatography (H:A 6:4, 1.5 cm x 20 cm).

The fraction R_f 0.55 yielded (*E*)-3-(3-hydroxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one as a light yellow solid[169] (0.350 g, 97%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.69 (1H, d, J = 3.9 Hz, H-5'), 8.15 (1H, d, J = 15.7 Hz, H-3), 8.13 (1H, d, J = 7.2 Hz, H-2'), 7.85 (1H, td, J = 7.7, 1.5 Hz, H-4'), 7.80 (1H, d, J = 15.7 Hz, H-2), 7.49 – 7.43 (1H, m, H-3'), 7.19 – 7.15 (3H, m, H-4", H-5", H-6"), 6.84 (1H, m, H-2") (Plate 10a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.5 (C-1), 156.3 (C-3"), 154.0 (C-1'), 148.7 (C-5'), 145.1 (C-3), 137.5 (C-3'), 136.6 (C-1"), 130.1 (C-5"), 127.2 (C-4'), 123.3 (C-2), 121.7 (C-6"), 121.1 (C-2'), 118.1 (C-2"), 115.2 (C-4") (Plate 10b).

IR (neat): ν_{max} = 3355.42, 1591.14, 980.45, 782.63, 665.89 cm^{-1}
Found (TOF MS ES) 248.0685, ($C_{14}H_{11}NO_2$ + Na) requires *m/z* 248.0687.

General procedure for the synthesis of aminoalkylated chalcones *via* the Mannich reaction

A mixture of the appropriate chalcone (1 eq.), paraformaldehyde (1.5 eq.), and the appropriate amine (2 eq.) was dissolved in EtOH (2 mL) and conc. HCl (5 drops). The reaction mixture was refluxed for 9 hours until TLC showed the disappearance of the starting material. The reaction mixture was quenched with solid $NaHCO_3$ and extracted with EtOAc (2 x 50 mL) and water (2 x 50 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure.

11. Synthesis of (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (41)

Compound (**41**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.609 g; 2.4 mmol), paraformaldehyde (0.145 g; 4.8 mmol), and piperidine (0.50 mL; 5.1 mmol) as starting

materials. The product was separated by column chromatography (T:A 5:5, 1.5 cm x 20 cm).

The fraction R_f 0.42 yielded (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**41**) as beige crystals[166] (0.520 g, 62%), mp 120-121 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.18 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.81 (1H, d, J = 15.5 Hz, H-3), 7.68 (1H, d, J = 15.5 Hz, H-2), 7.17 (1H, d, J = 1.5 Hz, H-2"), 7.16 (1H, dd, J = 7.5, 1.5 Hz, H-6"), 7.09 (1H, d, J = 7.5 Hz, H-5"), 7.07 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.91 (3H, s, OC**H$_3$**), 3.74 (2H, s, C**H$_2$**), 2.53 (4H, br s, H-2'", H-6'"), 1.63 (4H, m, H-3'", H-5'"), 1.52 (2H, br s, H-4'") (Plate 11a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 188.2 (C-1), 164.5 (C-4'), 159.6 (C-3"), 144.1 (C-3), 136.5 (C-1"), 132.1 (C-1'), 131.6 (C-2', C-6'), 130.0 (C-5"), 125.6 (C-4"), 122.3 (C-2), 120.7 (C-2"), 115.6 (C-6"), 114.7 (C-3', C-5'), 62.4 (**C**H_2), 56.0 (O**C**H_3), 54.5 (C-2'", C-6'"), 26.7 (C-3'", C-5'"), 24.6 (C-4'") (Plate 11b).

IR (KBr): ν_{max} = 2945.44, 2159.13, 2031.94, 1598.90, 1256.25 cm^{-1}
Found (EI) M^+ 351.1826, $C_{22}H_{25}NO_3$ requires 351.1824.
HPLC purity 99.1%, t_R = 1.54 min.

12. Synthesis of (*E*)-3-(3-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl)-1-phenylprop-2-en-1-one (42)

Compound (**42**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one (**40**) (0.485 g; 2.2 mmol), paraformaldehyde (0.060 g; 2.0 mmol), and pyrrolidine (0.17 mL; 2.1 mmol) as starting materials. The product was separated by column chromatography (T:A 6:4, 1.5 cm x 20 cm).

The fraction R_f 0.52 yielded (*E*)-3-(3-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl)-1-phenylprop-2-en-1-one (**42**) as a yellow solid (0.520, 84%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.02 (2H, d, J = 8.5 Hz, H-2', H-6'), 7.75 (1H, d, J = 15.7 Hz, H-3), 7.58 (1H, t, J = 7.4 Hz, H-4'), 7.53 – 7.47 (2H, t, J = 7.5 Hz, H-3', H-5', 1H, d, J = 15.7 Hz, H-2), 7.13 (1H, d, J = 1.5 Hz, H-2"), 7.04 (1H, dd J = 7.7, 1.5 Hz, H-6"), 7.02 (1H, d, J = 7.7 Hz, H-5"), 3.86 (2H, s, C**H$_2$**), 2.65 (4H, br s, H-2'", H-5'"), 1.89 – 1.84 (4H, m, H-3'", H-4'") (Plate 12a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 190.6 (C-1), 158.5 (C-3"), 144.9 (C-3), 138.3 (C-1'), 135.3 (C-1"), 132.7 (C-4'), 128.6 (C-2', C-6'), 128.5 (C-3', C-5'), 128.3 (C-5"), 125.5 (C-4"), 121.7 (C-2), 120.0 (C-6"), 114.9 (C-2"), 58.7 (**C**H_2), 53.6 (H-2'", H-5'"), 23.7 (H-3'", H-4'") (Plate

12b).

IR (neat): ν_{max} = 2923.01, 1054.87, 1033.13, 1014.89, 776.85, 693.13 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 308.1652, ($C_{20}H_{21}NO_2 + H^+$) requires *m/z* 308.1651.
HPLC purity 99.9%, t_R = 1.54 min.

13. Synthesis of (*E*)-3-(4-hydroxy-3-methoxy-5-(piperidin-1-ylmethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (43)

Compound (**43**) was synthesized according to the general procedure using (*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**102**) (0.568 g; 2.0 mmol), paraformaldehyde (0.075 g; 2.5 mmol), and piperidine (0.25 mL; 2.5 mmol) as starting materials. Column chromatography (T:EtOAc:A 6:2:2, 1.5 cm x 20 cm) yielded the pure product, which was crystallized from EtOH.

The fraction R_f 0.46 yielded (*E*)-3-(4-hydroxy-3-methoxy-5-(piperidin-1-ylmethyl)phenyl)-1-(4-methoxy-phenyl)prop-2-en-1-one (**43**) as brown crystals[166] (0.317 g, 42%), mp 149-150 ˚C. ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.12 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.71 (1H, d, J = 15.6 Hz, H-3), 7.68 (1H, d, J = 15.6 Hz, H-2), 7.38 (1H, d, J = 1.5 Hz, H-2''), 7.13 (1H, d, J = 1.5 Hz, H-6''), 7.06 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.91 (3H, s, OC**H$_3$**), 3.89 (3H, s, OC**H$_3$**), 3.76 (2H, s, C**H$_2$**), 2.56 (4H, br s, H-2''', H-6'''), 1.65 (4H, m, H-3''', H-5'''), 1.52 (2H, br s, H-4''') (Plate 13a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 188.1 (C-1), 164.2 (C-4'), 151.8 (C-4''), 149.3 (C-1''), 144.9 (C-3''), 132.4 (C-3), 131.4 (C-2', C-6'), 126.8 (C-1'), 123.8 (C-6''), 123.1 (C-5''), 119.4 (C-2), 114.6 (C-3', C-5'), 112.0 (C-2''), 62.0 (**C**H_2), 56.4 (O**C**H_3), 55.9 (O**C**H_3), 54.4 (C-2''', C-6'''), 26.6 (C-3''', C-5'''), 24.6 (C-4''') (Plate 13b).

IR (KBr): ν_{max} = 2939.18, 1650.69, 1603.79, 1157.02 cm^{-1}
Found (EI) M^+ 381.0589, $C_{21}H_{23}NO_4$ requires 353.19.
HPLC purity 96.1%, t_R = 1.57 min.

14. Synthesis of (*E*)-3-(3-hydroxy-4-(morpholinomethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (44)

Compound (**44**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.483 g; 1.9 mmol),

paraformaldehyde (0.069 g; 2.3 mmol), and morpholine (0.30 mL; 3.4 mmol) as starting materials. The mixture was placed in the fridge and crystallization from EtOH was attempted. After 2 days, crystals started to form and NMR proved the presence of (*E*)-3-(3-hydroxy-4-(morpholinomethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**44**).

(*E*)-3-(3-hydroxy-4-(morpholinomethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**44**) was yielded as brown crystals[166] (0.312 g, 47%), mp 131-132 ˚C. ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.03 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.6 Hz, H-3), 7.51 (1H, d, J = 15.6 Hz, H-2), 7.14 (1H, d, J = 1.4 Hz, H-2"), 7.06 (1H, dd, J = 7.7, 1.5 Hz, H-6"), 7.03 (1H, d, J = 7.7 Hz, H-5"), 6.98 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.89 (3H, s, OC**H$_3$**), 3.77 (4H, br s, H-2"', H-6"'), 3.75 (2H, s, C**H$_2$**), 2.59 (4H, br s, H-3"', H-5"') (Plate 14a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 188.7 (C-1), 163.4 (C-4'), 157.9 (C-3"), 143.7 (C-3), 136.1 (C-1"), 131.2 (C-1'), 130.8 (C-2', C-6'), 129.3 (C-5"), 123.3 (C-4"), 121.9 (C-2), 120.3 (C-6"), 115.0 (C-2"), 113.9 (C-3', C-5'), 66.8 (C-3"', C-5"'), 61.7 (O**C**H$_3$), 55.5 (**C**H$_2$), 53.0 (C-2"', C-6"') (Plate 14b).

IR (KBr): ν_{max} = 2159.21, 1655.39, 1593.98, 1269.53 cm^{-1}
Found (EI) M^+ 353.1619, $C_{21}H_{23}NO_4$ requires 353.1617.

15. Synthesis of (*E*)-3-(4-hydroxy-3-((4-methylpiperazin-1-yl)methyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (45)

Compound (**45**) was synthesized according to the general procedure using (*E*)-3-(4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**101**) (0.503 g; 2.0 mmol), paraformaldehyde (0.060 g; 2.0 mmol), and 1-methylpiperazine (0.22 mL; 2.0 mmol). The crude product was separated on 15 silica plates (EtOAc:EtOH:A 6:2:2) as starting materials. The product was stubborn towards crystallization; however we did manage to get a few crystals.

The fraction R_f 0.21 yielded (*E*)-3-(4-hydroxy-3-((4-methylpiperazin-1-yl)methyl)phenyl)-1-(4-methoxy-phenyl)prop-2-en-1-one (**45**) as yellow crystals (0.365 g, 50%), mp 124-125 ˚C. ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.03 (2H, d, J = 8.8 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.5 Hz, H-3), 7.50 (1H, dd, J = 8.4, 2.1 Hz, H-6"), 7.39 (1H, dd, J = 15.5 Hz, H-2), 7.30 (1H, d, J = 1.8 Hz, H-2"), 6.97 (2H, d, J = 8.9 Hz, H-3', H-5'), 6.85 (1H, d, J = 8.4 Hz, H-5"), 3.89

(3H, s, OC**H$_3$**), 3.77 (2H, s, C**H$_2$**), 2.64 (8H, br s, H-2''', H-3''', H-5''', H-6'''), 2.32 (3H, s, N-C**H$_3$**) (Plate 15a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 188.7 (C-1), 163.2 (C-4'), 160.4 (C-4''), 144.1 (C-3), 131.5 (C-1'), 130.7 (C-2', C-6'), 129.6 (C-6''), 129.2 (C-1''), 126.4 (C-2''), 121.5 (C-3''), 118.8 (C-2), 116.8 (C-5''), 113.8 (C-3', C-5'), 61.2 (**C**H$_2$), 55.5 (O**C**H$_3$), 54.8 (C-3''', C-5'''), 52.5 (C-2''', C-6'''), 45.9 (N-**C**H$_3$) (Plate 15b).

IR (neat): ν_{max} = 2974.89, 1580.95, 1251.89, 831.97 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 367.2027, ($C_{22}H_{26}N_2O_3 + H^+$) requires *m/z* 367.2022.
HPLC purity 98.2%, t_R = 1.50 min.

16. Synthesis of (*E*)-3-(3-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (46)

Compound (**46**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.490 g; 1.9 mmol), paraformaldehyde (0.063 g; 2.1 mmol), and pyrrolidine (0.17 mL; 2.1 mmol) as starting materials. The product was crystallized from EtOH in good yield without any chromatography.

The title compound was obtained as light yellow crystals (R_f = 0.45, 0.260 g, 40%), mp 120-121 ˚C. ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.03 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.6 Hz, H-3), 7.50 (1H, d, J = 15.6 Hz, H-2), 7.13 (1H, d, J = 1.4 Hz, H-2''), 7.03 (1H, dd, J = 7.7, 1.4 Hz, H-6''), 7.01 (1H, d J = 7.7 Hz, H-5''), 6.98 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.89 (3H, s, OC**H$_3$**), 3.85 (2H, s, C**H$_2$**), 2.65 (4H, br s, H-2''', H-5'''), 1.89 – 1.85 (4H, m, H-3''', H-4''') (Plate 16a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 188.8 (C-1), 163.4 (C-4'), 158.5 (C-3''), 144.0 (C-3), 135.6 (C-1''), 131.3 (C-1'), 130.8 (C-2', C-6'), 128.3 (C-5''), 125.2 (C-4''), 121.5 (C-2), 119.9 (C-6''), 114.8 (C-2''), 113.8 (C-3', C-5'), 58.7 (**C**H$_2$), 55.5 (O**C**H$_3$), 53.6 (C-2''', C-5'''), 23.7 (C-3''', C-4''') (Plate 16b).

IR (neat): ν_{max} = 2829.13, 1572.24, 1259.35, 1167.41, 811.38, 560.09 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 338.1757, ($C_{21}H_{23}NO_3 + H^+$) requires *m/z* 338.1756.
HPLC purity 99.7%, t_R = 1.54 min.

17. Synthesis of (*E*)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (47)

Compound (**47**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.350 g; 1.38 mmol), paraformaldehyde (0.057 g; 1.87 mmol), and 1-ethylpiperazine (0.17 mL; 1.31 mmol) as starting materials. The title compound was crystallized from EtOH.

(*E*)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**47**) was obtained as yellow crystals (R_f = 0.55, 0.289 g, 58%), mp 120-121 ˚C. ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.04 (2H, d, J = 8.9 Hz, H-2', H-6'), 7.73 (1H, d, J = 15.6 Hz, H-3), 7.51 (1H, d, J = 15.6 Hz, H-2), 7.13 (1H, d, J = 1.3 Hz, H-2''), 7.05 (1H, dd, J = 1.5, 7.7 Hz, H-6''), 7.03 (1H, d, J = 7.7 Hz, H-5''), 6.98 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.89 (3H, s, OC**H$_3$**), 3.75 (2H, s, C**H$_2$**), 2.83 (8H, br s, H-2''', H-3''', H-5''', H-6'''), 2.45 (2H, q, 7.2 Hz, C**H$_2$**-CH_3), 1.09 (3H, t, J = 7.2 Hz, CH_2-C**H$_3$**) (Plate 17a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 188.7 (C-1), 163.4 (C-4'), 158.1 (C-3''), 143.8 (C-3), 135.8 (C-1''), 131.2 (C-1'), 130.8 (C-2', C-6'), 129.1 (C-5''), 123.9 (C-4''), 121.7 (C-2), 120.1 (C-6''), 114.9 (C-2''), 113.8 (C-3', C-5'), 61.2 (**C**H_2), 55.5 (O**C**H_3), 52.6 (C-3''', C-5'''), 52.5 (C-2''', C-6'''), 52.1 (**C**H_2-CH_3), 12.0 (CH_2-**C**H_3) (Plate 17b).

IR (KBr): ν_{max} = 2958.22, 1055.03, 1033.15, 1016.57 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 381.2180, ($C_{23}H_{28}N_2O_3 + H^+$) requires *m/z* 381.2178.
HPLC purity 98.9%, t_R = 1.52 min.

18. Synthesis of (*E*)-3-(4-((dimethylamino)methyl)-3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (48)

Compound (**48**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.155 g; 0.6 mmol), paraformaldehyde (0.032 g; 1.1 mmol), and dimethylamine (0.10 mL; 1.5 mmol) as starting materials. Column chromatography (T:A 7:3, 1.5 cm x 15 cm) yielded the pure product, which was crystallized from EtOH.

The fraction R_f 0.24 yielded (*E*)-3-(4-((dimethylamino)methyl)-3-hydroxyphenyl)-1-(methoxyphenyl)prop-2-en-1-one (**48**) as yellow crystals[166] (0.097 g, 52%), mp 135-136 ˚C.

^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.19 (2H, d, J = 9.0 Hz, H-2', H-6'), 7.83 (1H, d, J = 15.5 Hz, H-3), 7.69 (1H, d, J = 15.5 Hz, H-2), 7.20 (1H, d, J = 1.6 Hz, H-2"), 7.18 (1H, dd, J = 7.7, 1.6 Hz, H-6"), 7.10 (1H, d, J = 7.6 Hz, H-5"), 7.08 (2H, d, J = 8.9 Hz, H-3', H-5'), 3.91 (3H, s, OC**H$_3$**), 3.72 (2H, s, C**H$_2$**), 2.34 (6H, s, 2 x N-C**H$_2$**) (Plate 18a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 188.1 (C-1), 164.5 (C-4'), 159.6 (C-3"), 144.1 (C-3), 136.6 (C-1"), 132.0 (C-1'), 131.6 (C-2", C-6"), 129.8 (C-5"), 125.9 (C-4"), 122.3 (C-2), 120.7 (C-6"), 115.5 (C-2"), 114.7 (C-3', C-5'), 63.0 (**C**H_2), 55.9 (O**C**H_3), 44.6 (2 x N-**C**H_3) (Plate 18b).

IR (neat): ν_{max} = 2978.95, 1592.27, 1181.27, 815.19 cm^{-1}
Found (EI) M^+ 311.1521, $C_{19}H_{21}NO_3$ requires 311.1510.
HPLC purity 99.8%, t_R = 1.52 min.

19. Synthesis of (*E*)-3-(3-((dimethylamino)methyl)-4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (49)

Compound (**49**) was synthesized according to the general procedure using (*E*)-3-(4-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**101**) (0.131 g; 0.5 mmol), paraformaldehyde (0.021 g; 0.7 mmol), and dimethylamine (0.04 mL; 0.6 mmol) as starting materials. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The title compound was crystallized from EtOAc and hexane without any chromatography.

(*E*)-3-(3-((dimethylamino)methyl)-4-hydroxyphenyl)-1-(4-methoxyphenyl)-prop-2-en-1-one (**49**) was obtained as bright yellow crystals (0.089 g, 58%), mp 181-182 ˚C. ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.03 (2H, d, J = 8.8 Hz, H-2', H-6'), 7.74 (1H, d, J = 15.5 Hz, H-3), 7.51 (1H, dd, J = 2.1, 8.4 Hz, H-6"), 7.39 (1H, d, J = 15.5 Hz, H-2), 7.27 (1H, d, J = 1.8 Hz, H-2"), 6.98 (2H, d, J = 8.9 Hz, H-3', H-5'), 6.86 (1H, d, J = 8.4 Hz, H-5"), 3.89 (3H, s, OC**H$_3$**), 3.70 (2H, s, C**H$_2$**), 2.36 (6H, s, 2 x N-C**H$_3$**) (Plate 19a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 188.8 (C-1), 163.2 (C-4'), 160.9 (C-4"), 144.3 (C-3), 131.5 (C-1'), 130.7 (C-2", C-6"), 129.4 (C-6'), 129.0 (C-1"), 126.2 (C-2"), 122.2 (C-3"), 118.7 (C-2), 116.8 (C-5"), 113.7 (C-3', C-5'), 62.6 (**C**H_2), 55.5 (O**C**H_3), 44.5 (2 x N-**C**H_3) (Plate 19b).

IR (neat): ν_{max} = 3010.24, 2329.75, 1054.87, 1015.96, 976.05, 771.87 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 312.1598, ($C_{19}H_{21}NO_3$ + H^+) requires *m/z* 312.1600.

HPLC purity 99.9%, t_R = 1.53 min.

20. Synthesis of (*E*)-3-(4-hydroxy-3-(piperidin-1-ylmethyl)phenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (50)

Compound (**50**) was synthesized according to the general procedure using (*E*)-3-(4-hydroxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (0.100 g; 0.34 mmol), paraformaldehyde (0.025 g; 0.83 mmol), and piperidine (0.04 mL; 0.6 mmol). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude reaction mixture was separated by column chromatography (T:A 5:5, 1.5 cm x 15 cm).

The fraction R_f 0.43 yielded (*E*)-3-(4-hydroxy-3-(piperidin-1-ylmethyl)phenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**50**) as a yellow solid (0.095 g, 72%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.84 (1H, dd, J = 8.5, 2.2 Hz, H-6''), 7.71 (2H, d, J = 15.6 Hz, H-3, d, J = 2.2 Hz, H-2''), 7.66 (2H, d, J = 8.3 Hz, H-2', H-6'), 7.59 (2H, d, J = 8.3 Hz, H-3', H-5'), 7.53 (1H, d, J = 15.6 Hz, H-2), 6.81 (1H, d, J = 8.3 Hz, H-5''), 3.71 (2H, s, C**H$_2$**), 2.97 – 2.03 (4H, br s, H-2''', H-6'''), 1.57 – 1.41 (6H, br s, H-3''', H-4''', H-5''') (Plate 20a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.0 (C-1), 163.8 (C-4''), 141.5 (C-3), 138.6 (C-1'), 131.6 (1C, q, $^2J_{C\text{-}F}$ = 32.8 Hz, C-4'), 130.3 (C-6''), 129.7 (C-1''), 129.0 (C-2''), 128.4 (C-2', C-6'), 125.9 (2C, q, $^3J_{C\text{-}F}$ = 3.9 Hz, C-3', C-5'), 124.2 (C-3''), 123.9 (1C, q, $^1J_{C\text{-}F}$ = 272.2 Hz, **C**F_3), 121.8 (C-2), 116.1 (C-5''), 61.8 (**C**H_2), 53.8 (C-2''', C-6'''), 25.7 (C-3''', C-5'''), 23.8 (C-4''') (Plate 20b and 20c).

Found (TOF MS ES) $[M+H]^+$ 390.1607, ($C_{22}H_{22}F_3NO_2 + H^+$) requires *m/z* 390.1609.

21. Synthesis of (*E*)-1-(4-bromophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (51)

Compound (**51**) was synthesized according to the general procedure using (*E*)-1-(4-bromophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**104**) (0.100 g; 0.33 mmol), paraformaldehyde (0.020 g; 0.66 mmol), and piperidine (0.04 mL; 0.6 mmol) as starting materials. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude reaction mixture was separated by column chromatography (T:A 5:5, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded (*E*)-1-(4-bromophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (**51**) as a bright yellow solid (0.118 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.81 (2H, d, J = 8.5 Hz, H-2', H-6'), 7.67 (1H, d, J = 15.6 Hz, H-3), 7.57 (1H, d, J = 8.5 Hz, H-3', H-5'), 7.36 (2H, d, J = 15.6 Hz, H-2), 7.04 (1H, d, J = 1.2 Hz, H-2''), 6.96 (1H, dd, J = 7.7, 1.2 Hz, H-6''), 6.93 (1H, d, J = 7.7 Hz, H-5''), 3.63 (2H, s, C**H$_2$**), 2.61 (4H, br s, H-2''', H-6'''), 1.58 (6H, br s, H-3''', H-4''', H-5''') (Plate 21a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.4 (C-1), 158.6 (C-3''), 145.5 (C-3), 137.0 (C-1'), 135.1 (C-1''), 131.9 (C-2', C-6'), 131.8 (C-5''), 130.0 (C-3', C-5'), 129.0 (C-4'), 124.9 (C-4''), 121.1 (C-2), 120.2 (C-6''), 115.0 (C-2''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 25.8 (C-3''', C-5'''), 23.9 (C-4''') (Plate 21b).

Found (TOF MS ES) $[M+H]^+$ 400.0907, ($C_{21}H_{22}BrNO_2 + H^+$) requires *m/z* 400.0912.

22. Synthesis of (*E*)-1-(4-ethylphenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (52)

Compound (**52**) was synthesized according to the general procedure using (*E*)-1-(4-ethylphenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (0.100 g; 0.40 mmol), paraformaldehyde (0.020 g; 0.66 mmol), and piperidine (0.04 mL; 0.6 mmol) as starting materials. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.50 yielded (*E*)-1-(4-ethylphenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (**52**) as a bright yellow solid (0.088 g, 63%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.88 (2H, d, J = 8.2 Hz, H-2', H-6'), 7.66 (1H, d, J = 15.6 Hz, H-3), 7.42 (1H, d, J = 15.6 Hz, H-2), 7.25 (2H, d, J = 8.2 Hz, H-3', H-5'), 7.05 (1H, d, J = 1.4 Hz, H-2''), 6.96 (1H, dd, J = 7.7, 1.4 Hz, H-6''), 6.92 (1H, d, J = 7.7 Hz, H-5''), 3.63 (2H, s, C**H$_2$**), 3.01 – 2.10 (6H, m, H-2''', H-6''', C**H$_2$**-CH_3), 1.61 – 1.40 (6H, m, H-3''', H-4''', H-5'''), 1.23 – 1.18 (3H, s, CH_2-C**H$_3$**) (Plate 22a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 190.2 (C-1), 158.5 (C-3''), 149.8 (C-4'), 144.5(C-3), 136.0 (C-1''), 135.5 (C-1'), 128.9 (C-5''), 128.8 (C-2', C-6'), 128.1 (C-3', C-5'), 124.5 (C-4''), 121.8 (C-2), 120.1 (C-6''), 114.9 (C-2''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 29.0 (**C**H_2-CH_3), 25.8 (C-3''', C-5'''), 23.9 (C-4'''), 15.2 (CH_2-**C**H_3) (Plate 22b).

IR (neat): ν_{max} = 2964.17, 1596.07, 1261.07, 986.96, 815.58 cm^{-1}

Found (TOF MS ES) $[M+H]^+$ 350.2117, ($C_{23}H_{27}NO_2 + H^+$) requires *m/z* 350.2120.

23. Synthesis of (*E*)-1-(4-fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (53)

Compound (**53**) was synthesized according to the general procedure using (*E*)-1-(4-fluorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**103**) (0.100 g; 0.41 mmol), paraformaldehyde (0.052 g; 1.73 mmol), and piperidine (0.18 mL; 1.84 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.52 yielded (*E*)-1-(4-fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one (**53**) as a yellow solid (0.118 g; 85%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.97 (2H, dd, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 5.4 Hz, H-2', H-6'), 7.65 (1H, d, J = 15.6 Hz, H-3), 7.39 (1H, d, J = 15.6 Hz, H-2), 7.24 – 7.03 (2H, H-2", H-6"), 7.09 (2H, t, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 8.6 Hz, H-3', H-5'), 7.05 (1H, d, J = 7.8 Hz, H-5"), 3.68 (2H, s, C**H$_2$**), 1.66 – 1.13 (10H, H-2'", H-3'", H-4'", H-5'", H-6'") (Plate 23a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 192.2 (C-1), 188.9 (C-3"), 165.6 (1C, d, $^1J_{C-F}$ = 254.2 Hz, C-4'), 158.9 (C-3), 158.5 (C-1"), 145.0 (C-1'), 134.6 (1C, d, $^4J_{C-F}$ = 2.8 Hz, C-1'), 131.1 (2C, d, $^3J_{C-F}$ = 9.0 Hz, C-2', C-6'), 121.3 (C-5"), 120.5 (C-4"), 120.1 (C-2), 116.8 (C-6"), 115.7 (2C, d, $^2J_{C-F}$ = 21.7 Hz, C-3', C-5'), 115.1 (C-2"), 53.9 – 23.7 (**C**H_2, C-2'", C-3'", C-4'", C-5'", C-6'") (Plate 23b and 23c).

IR (neat): ν_{max} = 2943.48, 1599.27, 1588.95, 1272.49, 984.97, 810.90, 570.78 cm^{-1}

Found (TOF MS ES) $[M+H]^+$ 340.1711, ($C_{21}H_{22}FNO_2 + H^+$) requires *m/z* 340.1713.

24. Synthesis of (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (54)

Compound (**54**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**108**) (0.200 g; 0.89 mmol), paraformaldehyde (0.052 g; 1.73 mmol), and piperidine (0.18 mL; 1.82 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.52 yielded (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(pyridin-2-

yl)prop-2-en-1-one (**54**) as a light oil (0.180 g, 63%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 8.67 (1H, d, J = 3.9 Hz, H-5'), 8.18 (1H, d, J = 15.6 Hz, H-3), 8.11 (1H, d, J = 7.8 Hz, H-2'), 7.80 (1H, d, J = 15.6 Hz, H-2), 7.80 – 7.79 (1H, m, H-4'), 7.45 – 7.37 (1H, m, H-3'), 7.12 (1H, d, J = 1.4 Hz, H-2''), 7.06 (1H, dd, J = 7.7, 1.4 Hz, H-6''), 6.92 (1H, d, J = 7.7 Hz, H-5''), 3.63 (2H, s, C**H$_2$**), 3.02 – 1.20 (10H, m, H-2''', H-3''', H-4''', H-5''', H-6''') (Plate 24a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.6 (C-1), 158.4 (C-3''), 154.3 (C-1'), 148.9 (C-5'), 144.9 (C-1''), 137.0 (C-3), 135.7 (C-4'), 128.9 (C-5''), 126.8 (C-3'), 124.6 (C-4''), 122.9 (C-2'), 120.6 (C-2), 120.1 (C-6''), 115.8 (C-2''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 25.8 (C-3''', C-5'''), 23.9 (C-4''') (Plate 24b).

IR (neat): ν_{max} = 2937.25, 1276.26, 986.06, 740.03 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 323.1755, ($C_{20}H_{22}N_2O_2 + H^+$) requires *m/z* 323.1760.

25. Synthesis of (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (55)

Compound (**55**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (**107**) (0.150 g; 0.70 mmol), paraformaldehyde (0.050 g; 1.67 mmol), and piperidine (0.18 mL; 1.82 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.52 yielded (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (**55**) as a light oil (0.195 g, 90%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.68 (1H, d, J = 15.6 Hz, H-3), 7.24 (1H, d, J = 15.6 Hz, H-2), 7.05 (1H, d, J = 1.5 Hz, H-2''), 7.04 – 7.02 (1H, m, H-4'), 6.99 (1H, t, J = 1.6 Hz, H-3'), 6.95 (1H, dd, J = 7.7, 1.5 Hz, H-6''), 6.92 (1H, d, J = 7.7 Hz, H-5''), 6.31 – 6.26 (1H, m, H-2'), 3.63 (3H, s, C**H$_2$**), 3.00 – 1.30 (10H, H-2''', H-3''', H-4''', H-5''', H-6''') (Plate 25a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 179.0 (C-1), 158.5 (C-3''), 142.4 (C-3), 129.1 (C-1''), 128.9 (C-1'), 128.2 (C-5''), 125.3 (C-2'), 125.1 (C-4'), 121.6 (C-2), 120.0 (C-6''), 116.2 (C-3'), 114.8 (C-2''), 111.1 (C-4''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 25.8 (C-3''', C-5'''), 23.9 (C-4''') (Plate 25b).

Found (TOF MS ES) $[M+H]^+$ 311.1682, ($C_{19}H_{22}N_2O_2 + H^+$) requires *m/z* 311.1681.

26. Synthesis of (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (56)

Compound (**56**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**106**) (0.100 g; 0.43 mmol), paraformaldehyde (0.045 g; 1.50 mmol), and piperidine (0.18 mL; 1.82 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.52 yielded (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**56**) as a light oil (0.133 g; 95%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 9.84 (1 x OH), 7.79 (1H, dd, J = 3.8, 1.1 Hz, H-4'), 7.71 (1H, d, J = 15.5 Hz, H-3), 7.61 (1H, d, J = 4.9, 1.1 Hz, H-2'), 7.32 (1H, d, J = 15.5 Hz, H-2), 7.12 (1H, dd, J = 4.9, 3.8 Hz, H-3'), 7.06 (1H, d, J = 1.4 Hz, H-2''), 6.96 (1H, dd, J = 7.7, 1.4 Hz, H-6''), 6.93 (1H, d, J = 7.7 Hz, H-5''), 5.23 (2H, s, C**H$_2$**), 2.10 – 1.10 (10H, H-2''', H-3''', H-4''', H-5''', H-6''') (Plate 26a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 182.1 (C-1), 158.5 (C-3''), 145.7 (C-3), 144.1 (C-1'), 135.2 (C-1''), 133.8 (C-4'), 131.7 (C-3'), 129.0 (C-2'), 128.2 (C-5''), 124.8 (C-4''), 121.3 (C-2), 120.2 (C-6''), 114.8 (C-2''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 25.8 (C-3''', C-5'''), 23.9 (C-4''') (Plate 26b).

IR (neat): ν_{max} = 1646.84, 1592.91, 1274.47, 980.06, 719.30 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 328.1372, ($C_{19}H_{21}NO_2S + H^+$) requires *m/z* 328.1371.
HPLC purity 96.5%, t_R = 3.00 min.

27. Synthesis of (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-*p*-tolylprop-2-en-1-one (57)

Compound (**57**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-p-tolylprop-2-en-1-one (**105**) (0.100 g; 0.42 mmol), paraformaldehyde (0.035 g; 1.16 mmol), and piperidine (0.15 mL; 1.52 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.50 yielded (*E*)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-p-tolylprop-2-en-1-one (**57**) as a colourless oil (0.090 g; 64%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.85 (2H, d, J = 8.2 Hz, H-2', H-6'), 7.66 (1H, d, J = 15.6 Hz, H-3), 7.42 (1H, d, J = 15.6 Hz, H-2), 7.22 (2H, d, J = 7.9 Hz, H-3', H-5'), 7.04 (1H, d, J = 1.5 Hz, H-2''), 6.95 (1H,

dd, J = 7.7, 1.5 Hz, H-6''), 6.91 (1H, d, J = 7.7 Hz, H-5''), 3.62 (2H, s, C**H$_2$**), 3.15 – 2.10 (4H, br s, H-2''', H-6'''), 2.35 (3H, s, C**H$_3$**), 1.57 (4H, s, H-3''', H-5'''), 1.42 (2H, br s, H-4''') (Plate 27a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 190.1 (C-1), 158.5 (C-3''), 144.4 (C-3), 143.6 (C-4'), 135.7 (C-1''), 135.5 (C-1'), 129.3 (C-2', C-6'), 128.9 (C-5''), 128.7 (C-3', C-5'), 124.6 (C-4''), 121.7 (C-2), 120.0 (C-6''), 114.9 (C-2''), 62.0 (**C**H_2), 54.0 (C-2''', C-6'''), 25.8 (C-3''', C-5'''), 23.9 (C-4'''), 21.7 (**C**H_3) (Plate 27b).

IR (neat): ν_{max} = 3226.34, 1649.55, 1584.48, 1403.77, 1107.42 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 336.1962, ($C_{22}H_{25}NO_2 + H^+$) requires *m/z* 336.1964.
HPLC purity 84.6%, t_R = 1.50 min.

General procedure for the synthesis of the dihydrochalcones

The chalcones previously synthesized were partially reduced by means of hydrogenation to obtain the dihydrochalcones as products. The appropriate chalcone (1 eq.) was dissolved in a 1:3 (v/v) solution of EtOAc:H_2O. $Pd(OH)_2/C$ (0.060 g) was added and the system flushed with hydrogen. The reaction mixture was left to stir at room temperature for 24–48 hrs under H_2 at atmospheric pressure. After completion of the reaction (TLC) the reaction mixture was filtered through silica gel, the filtrate extracted with EtOAc (2 x 50 mL) and washed with water (1 x 30 mL) and brine (1 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. Column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm) yielded the pure dihydrochalcones in good yield.

28. Synthesis of 1-(4-fluorophenyl)-3-(3-hydroxyphenyl)propan-1-one (109)

Compound (**109**) was synthesized according to the general procedure using (*E*)-1-(4-fluorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**103**) (0.200 g; 0.83 mmol), H_2 gas and $Pd(OH)_2/C$ (0.060 g).

The fraction R_f 0.50 yielded 1-(4-fluorophenyl)-3-(3-hydroxyphenyl)propan-1-one (**109**) as a colourless oil (0.179 g; 88%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.97 (2H, dd, $^3J_{H-H}$ = 8.1 Hz; $^4J_{H-F}$ = 5.8 Hz, H-2', H-6'), 7.15 (1H, t, J = 7.9 Hz, H-5''), 7.11 (2H, t, $^3J_{H-H}$ = 8.1 Hz; $^4J_{H-F}$ = 8.1 Hz, H-3', H-5'), 6.80 (1H, d, J = 7.5 Hz, H-4''), 6.74 (1H, s, H-2''), 6.69 (1H, d, J = 8.1 Hz, H-6''), 3.26 (2H, t, J = 7.5 Hz, H-2), 3.00 (2H, t, J = 7.5 Hz, H-3) (Plate 28a). ^{13}C NMR δ

(150 MHz, $CDCl_3$, Me_4Si) 198.1 (C-1), 165.8 (1C, d, $^1J_{C-F}$ = 254.6 Hz, C-4'), 155.8 (C-3"), 143.0 (C-1"), 133.2 (1C, d, $^4J_{C-F}$ = 2.9 Hz, C-1'), 130.7 (2C, d, $^3J_{C-F}$ = 9.5 Hz, C-2', C-6'), 129.8 (C-5"), 120.7 (C-6"), 115.8 (2C, d, $^2J_{C-F}$ = 21.9 Hz, C-3', C-5'), 115.4 (C-2"), 113.2 (C-4"), 40.2 (C-2), 29.9 (C-3) (Plate 28b and 28c).

29. Synthesis of 3-(3-hydroxyphenyl)-1-(thiophen-2-yl)propan-1-one (110)

Compound (**110**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**106**) (0.200 g; 0.87 mmol)), H_2 gas and $Pd(OH)_2/C$ (0.060 g).

The fraction R_f 0.50 yielded 3-(3-hydroxyphenyl)-1-(thiophen-2-yl)propan-1-one (**110**) as a light yellow oil (0.180 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.58 (1H, dd, J = 3.8, 1.1 Hz, H-4'), 7.51 (1H, dd, J = 4.9, 1.1 Hz, H-2'), 7.03 (1H, d, J = 7.9 Hz, H-3'), 6.99 (1H, dd, J = 4.9, 3.8 Hz, H-5"), 6.69 – 6.61 (3H, H-2", H-4", H-6"), 3.15 – 3.06 (2H, m, H-2), 2.92 – 2.85 (2H, m, H-3) (Plate 29a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 193.2 (C-1), 156.2 (C-3"), 143.8 (C-1'), 142.6 (C-1"), 134.2 (C-4'), 132.5 (C-2'), 129.8 (C-5"), 128.3 (C-3'), 120.5 (C-6"), 115.6 (C-2"), 113.5 (C-4"), 41.0 (C-2), 30.4 (C-3) (Plate 29b).

Found (TOF MS ES) 255.0454, ($C_{13}H_{12}SO_2$ + Na) requires *m/z* 255.0456.

30. Synthesis of 3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)propan-1-one (111)

Compound (**111**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (**107**) (0.200 g; 0.94 mmol), H_2 gas and $Pd(OH)_2/C$ (0.060 g).

The fraction R_f 0.50 yielded 3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)propan-1-one (**111**) as a light yellow oil (0.180 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 5.85 (1H, t, J = 7.8 Hz, H-5"), 5.75 – 5.71 (1H, m, H-4'), 5.64 (1H, s, H-2'), 5.52 – 5.40 (3H, m, H-2", H-4", H-6"), 4.97 (1H, s, H-3'), 1.81 (2H, t, J = 7.8 Hz, H-2), 1.70 (2H, t, J = 7.8 Hz, H-3) (Plate 30a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 190.5 (C-1), 156.0 (C-3"), 142.9 (C-1"), 131.6 (C-1'), 129.7 (C-5"), 125.5 (C-4'), 120.5 (C-6"), 117.2 (C-2'), 115.6 (C-2"), 133.3 (C-4"), 110.8 (C-3'), 39.4 (H-2), 30.8 (H-3) (Plate 30b).

Found (TOF MS ES) 238.0848, ($C_{13}H_{13}NO_2$ + Na) requires *m/z* 238.0850.

Synthesis of the aminoalkylated dihydrochalcones

31. Synthesis of 1-(4-fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)propan-1-one (60)

Compound (**60**) was synthesized according to the general procedure for the Mannich reaction given previously using 1-(4-fluorophenyl)-3-(3-hydroxyphenyl)propan-1-one (**109**) (0.100 g; 0.41 mmol), paraformaldehyde (0.024 g; 0.80 mmol), and piperidine (0.09 mL; 0.88 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.52 yielded 1-(4-fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)propan-1-one (**60**) as a light yellow oil (0.118 g, 84%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.97 (2H, dd, $^3J_{H-H}$ = 8.9 Hz; $^4J_{H-F}$ = 5.4 Hz, H-2', H-6'), 7.09 (2H, t, $^3J_{H-H}$ = 8.9 Hz; $^4J_{H-F}$ = 8.9 Hz, H-3', H-5'), 6.86 (1H, d, J = 7.6 Hz, H-5''), 6.69 (1H, d, J = 1.5 Hz, H-2''), 6.64 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.62 (2H, s, C**H$_2$**), 3.24 (2H, t, J = 7.6 Hz, H-2), 2.96 (2H, t, J = 7.6 Hz, H-3), 2.47 (4H, H-2''', H-6'''), 1.61 (6H, s, H-3''', H-4''', H-5''') (Plate 31a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 197.8 (C-1), 165.7 (1C, d, $^1J_{C-F}$ = 254.4 Hz, C-4'), 158.1 (C-3''), 141.7 (C-1''), 133.3 (1C, d, $^4J_{C-F}$ = 3.1 Hz, C-1'), 130.7 (2C, d, $^3J_{C-F}$ = 9.1 Hz, C-2', C-6'), 128.6 (C-5''), 119.5 (C-4''), 119.0 (C-6''), 115.8 (C-2''), 115.7 (2C, d, $^2J_{C-F}$ = 21.8 Hz, C-3', C-5'), 61.9 (**C**H$_2$), 53.9 (C-2''', C-6'''), 40.3 (C-2), 30.0 (C-3), 25.9 (C-3''', C-5'''), 24.0 (C-4''') (Plate 31b and 31c).

32. Synthesis of 3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(thiophen-2-yl)propan-1-one (61)

Compound (**61**) was synthesized according to the general procedure for the Mannich reaction given previously using 3-(3-hydroxyphenyl)-1-(thiophen-2-yl)propan-1-one (**110**) 0.100 g; 0.43 mmol), paraformaldehyde (0.026 g; 0.87 mmol), and piperidine (0.09 mL; 0.88 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(thiophen-2-

yl)propan-1-one (**61**) as a light yellow oil (0.084 g, 59%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.73 – 7.67 (1H, m, H-2'), 7.65 – 7.59 (1H, m, H-4'), 7.13 – 7.08 (1H, m, H-3'), 6.88 (1H, d, J = 7.6 Hz, H-5''), 6.71 (1H, d, J = 1.5 Hz, H-2''), 6.65 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.64 (2H, s, C**H$_2$**), 3.25 – 2.25 (4H, H-2''', H-6'''), 3.21 (2H, t, J = 7.5 Hz, H-2), 2.99 (2H, t, J = 7.5 Hz, H-3), 1.67 – 1.32 (6H, br s, H-3''', H-4''', H-5''') (Plate 32a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 192.4 (C-1), 158.1 (C-3''), 144.2 (C-1'), 141.7 (C-1''), 133.5 (C-4'), 131.9 (C-2'), 128.6 (C-5''), 128.1 (C-3'), 119.5 (C-6''), 119.0 (C-4''), 115.7 (C-2''), 61.8 (**C**H_2), 53.9 (C-2''', C-6'''), 41.1 (C-2), 30.2 (C-3), 25.8 (C-3''', C-5'''), 24.0 (C-4''') (Plate 32b).

IR (neat): ν_{max} = 2933.95, 1660.53, 1414.69, 857.22, 722.75 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 330.1522, ($C_{19}H_{23}NO_2S + Na^+$) requires *m/z* 330.1528.
HPLC purity 90.7%, t_R = 1.52 min.

33. Synthesis of 3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(1H-pyrrol-2-yl)propan-1-one (62)

Compound (**62**) was synthesized according to the general procedure for the Mannich reaction given previously using 3-(3-hydroxyphenyl)-1-(1H-pyrrol-2-yl)propan-1-one (**111**) (0.150 g; 0.70 mmol), paraformaldehyde (0.042 g; 1.40 mmol), and piperidine (0.15 mL; 1.50 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)-1-(1H-pyrrol-2-yl)propan-1-one (**62**) as a light yellow oil (0.128 g, 59%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.02 (1H, s, H-4'), 6.91- 6.88 (1H, m, H-2'), 6.87 (1H, d, J = 7.6 Hz, H-5''), 6.70 (1H, d, J = 1.5 Hz, H-2''), 6.65 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 6.28 – 6.23 (1H, m, H-3'), 3.63 (3H, s, C**H$_2$**), 3.12 – 2.93 (4H, m, H-3, H-2), 2.25 – 1.00 (10H, H-2''', H-3''', H-4''', H-5''', H-6''') (Plate 33a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 189.8 (C-1), 158.1 (C-3''), 141.9 (C-1''), 131.9 (C-1'), 128.5 (C-5''), 124.4 (C-4'), 119.5 (C-4''), 118.9 (C-6''), 116.1 (C-2'), 115.8 (C-2''), 110.7 (C-3'), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 39.6 (C-2), 30.5 (C-3), 25.9 (C-3''', C-5'''), 24.0 (C-4''') (Plate 33b).

IR (neat): ν_{max} = 3265.51, 2923.94, 1648.75, 1106.70, 756.09, 605.96 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 313.1913, ($C_{19}H_{24}N_2O_2 + H^+$) requires *m/z* 313.1916.

HPLC purity 94.2%, t_R = 1.51 min.

General procedure for the synthesis of the diarylpropanes

The chalcones previously synthesized were fully reduced by means of hydrogenation. The appropriate chalcone (1 eq.) was dissolved in a 1:3 (v/v) solution of EtOAc:H_2O. 10% aq. HCl (10 mL) with $Pd(OH)_2/C$ (0.060 g) was added and the system flushed with hydrogen. The reaction mixture was left to stir at room temperature for 48–72 hrs under H_2 at atomspheric pressure. After completion of the reaction (TLC) the reaction mixture was filtered through silica gel, the filtrate extracted with EtOAc (2 x 50 mL) and washed with water (1 x 30 mL) and brine (1 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. Column chromatography (H:EtOAc 7:3, 1.5 cm x 20 cm) yielded the pure diarylpropanes in good yield.

34. Synthesis of 3-(3-(4-methoxyphenyl)propyl)phenol (63)

Compound (**63**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**39**) (0.200 g; 0.80 mmol) as starting material.

The fraction R_f 0.55 yielded 3-(3-(4-methoxyphenyl)propyl)phenol (**63**) as a yellow oil[166] (0.185 g, 97%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.10 (1H, t, J = 8.0 Hz, H-5"), 7.06 (2H, d, J = 8.5, H-2', H-6'), 6.82 (2H, d, J = 8.6 Hz, H-3', H-5'), 6.72 (1H, d, J = 7.6 Hz, H-4"), 6.64 (1H, d, J = 1.5 Hz, H-2", 1H, H-6"), 3.76 (3H, s, OC**H$_3$**), 2.57 – 2.51 (4H, m, H-1, H-3), 1.89 – 18.3 (2H, m, H-2) (Plate 34a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.5 (C-4'), 155.6 (C-3"), 144.3 (C-1"), 134.5 (C-1'), 129.4 (C-5"), 129.3 (C-2', C-6'), 120.8 (C-6"), 115.4 (C-2"), 113.7 (C-3', C-5'), 112.7 (C-4"), 55.3 (O**C**H$_3$), 35.2 (C-3), 34.4 (C-1), 32.9 (C-2) (Plate 34b).

IR (KBr): ν_{max} = 2933.38, 1586.44, 1510.27, 1241.05 cm^{-1}
Found (EI) M^+ 242.1306, $C_{16}H_{18}O_2$ requires 242.1307.

35. Synthesis of 3-(3-phenylpropyl)phenol (112)

Compound (**112**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one (**40**) (1.000 g; 4.46 mmol) as starting material.

The fraction R_f 0.53 yielded 3-(3-phenylpropyl)phenol (**112**) as a yellow oil[170] (0.820 g, 87%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.29 – 6.59 (9H, H-2', H-3', H-4', H-5', H-6', H-2", H-4", H-5", H-6"), 2.59 (2H, t, J = 7.7 Hz, H-3), 2.54 (2H, t, J = 7.7 Hz, H-1), 1.93 – 1.84 (2H, m, H-2) (Plate 35a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.3 (C-3"), 144.3 (C-1"), 142.2 (C-1'), 129.5 (C-5"), 128.4 (C-3', C-5'), 128.3 (C-2', C-6'), 125.7 (C-4'), 121.0 (C-6"), 115.4 (C-2"), 112.7 (C-4"), 35.3 (C-3), 35.2 (C-1), 32.7 (C-2) (Plate 35b).

IR (KBr): ν_{max} = 2933.01, 1588.08, 1453.17, 1152.91, 694.14, 591.57 cm^{-1}
Found (TOF MS ES) $[M-H]^+$ 211.1120, ($C_{15}H_{16}O - H^+$) requires *m/z* 211.1123.

36. Synthesis of 3-(3-(thiophen-2-yl)propyl)phenol (113)

Compound (**113**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**106**) (0.200 g; 0.86 mmol) as starting material.

The fraction R_f 0.51 yielded 3-(3-(thiophen-2-yl)propyl)phenol (**113**) as a yellow oil (0.168 g, 89%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.11 (1H, t, J = 7.6 Hz, H-5"), 7.08 (1H, dd, J = 5.1, 1.2 Hz, H-4'), 6.88 (1H, dd, J = 5.1, 3.4 Hz, H-3'), 6.75 (1H, dd, J = 3.4, 1.1 Hz, H-2'), 6.74 – 6.71 (1H, m, H-6"), 6.64 – 6.59 (2H, m, H-2", H-4"), 2.81 (2H, t, J = 7.6 Hz, H-1), 2.59 (2H, t, J = 7.6 Hz, H-3), 2.00 – 1.91 (2H, m, H-2) (Plate 36a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.5 (C-3"), 145.1 (C-1'), 143.9 (C-1"), 129.5 (C-5"), 126.7 (C-3'), 124.2 (C-2'), 123.0 (C-4'), 121.1 (C-6"), 115.4 (C-2"), 112.8 (C-4"), 35.0 (C-2), 33.1 (C-3), 29.3 (C-1) (Plate 36b).

IR (neat): ν_{max} = 2929.86, 1587.50, 1454.40, 1153.41, 690.51 cm^{-1}
Found (TOF MS ES) $[M-H]^+$ 217.0690, ($C_{13}H_{14}OS - H^+$) requires m/z 217.0687.

[170]Shimizu, R.; Iwamura, H.; Fujita, T. *Journal of Agricultural and Food Chemistry* **1988**, *36(6)*, 1276-1283.

37. Synthesis of 3-(3-*p*-tolylpropyl)phenol (114)

Compound (**114**) was synthesized according to the general procedure using (*E*)-3-(3-hydroxyphenyl)-1-*p*-tolylprop-2-en-1-one (**105**) (0.100 g; 0.42 mmol) as starting material.

The fraction R_f 0.55 yielded 3-(3-*p*-tolylpropyl)phenol (**114**) as a yellow oil (0.075 g, 79%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.06 – 6.52 (8H, m, H-2', H-3', H-5', H-6', H-2", H-4", H-5", H-6"), 2.51 – 2.45 (4H, m, H-1, H-3), 2.22 (3H, s, C**H$_3$**), 1.81 (2H, p, J = 7.7 Hz, H-2) (Plate 37a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.6 (C-3"), 144.4 (C-1'), 139.2 (C-1"), 135.2 (C-4'), 129.5 (C-5"), 129.1 (C-2', C-6'), 128.4 (C-3', C-5'), 121.0 (C-6"), 115.5 (C-2"), 112.8 (C-4"), 35.3 (C-3), 35.0 (C-1), 32.9 (C-2), 21.1 (**C**H$_3$) (Plate 37b).

IR (neat): ν_{max} = 2923.88, 1587.93, 1454.17, 1154.23, 692.35 cm^{-1}
Found (TOF MS ES) $[M-H]^+$ 225.1278, ($C_{16}H_{18}O$ - H^+) requires *m/z* 225.1279.

38. Synthesis of 3-(3-(4-fluorophenyl)propyl)phenol (115)

Compound (**115**) was synthesized according to the general procedure using (*E*)-1-(4-fluorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**103**) (0.500 g; 2.07 mmol) as starting material.

The fraction R_f 0.50 yielded 3-(3-(4-fluorophenyl)propyl)phenol (**115**) as a yellow oil (0.410 g, 86%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.15 – 7.09 (1H, m, H-5"), 7.09 (2H, dd, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 5.5 Hz, H-2', H-6'), 6.94 (2H, t, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 8.6 Hz, H-3', H-5'), 6.73 (1H, d, J = 7.6 Hz, H-4"), 6.68 – 6.64 (2H, m, H-2", H-6"), 2.59 – 2.56 (2H, m, H-1), 2.56 – 2.53 (2H, m, H-3), 1.91 – 1.84 (2H, m, H-2) (Plate 38a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 161.3 (1C, d, $^1J_{C-F}$ = 242.8 Hz, C-4'), 155.7 (C-3"), 144.1 (C-1"), 137.9 (1C, d, $^4J_{C-F}$ = 3.2 Hz, C-1'), 129.8 (2C, d, $^3J_{C-F}$ = 7.8 Hz, C-2', C-6'), 129.6 (C-5"), 120.9 (C-6"), 115.5 (C-2"), 115.1 (2C, d, $^2J_{C-F}$ = 20.9 Hz, C-3', C-5'), 112.9 (C-4"), 35.2 (C-1), 34.6 (C-3), 32.9 (C-2) (Plate 38b and 38c). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -117.9 (s, F) (Plate 38d).

IR (neat): ν_{max} = 2938.38, 1508.14, 1218.37, 1154.84, 834.11, 696.82 cm^{-1}

39. Synthesis of 4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (116)

Compound (**116**) was synthesized according to the general procedure using (*E*)-3-(4-hydroxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (0.500 g; 1.71 mmol) as starting material.

The fraction R_f 0.50 yielded 4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (**116**) as a colourless oil (0.398 g, 83%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.45 (2H, d, J = 8.0 Hz, H-3', H-5'), 7.19 (2H, d, J = 8.0 Hz, H-2', H-6'), 6.96 (2H, d, J = 8.5 Hz, H-2", H-6"), 6.69 (2H, d, J = 8.5 Hz, H-3", H-5"), 2.62 – 2.57 (2H, m, H-1), 2.52 – 2.48 (2H, m, H-3), 1.88 – 1.81 (2H, m, H-2) (Plate 39a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 153.7 (C-4"), 146.5 (C-1'), 134.0 (C-1"), 129.5 (C-2", C-6"), 128.7 (C-2', C-6'), 128.1 (1C, q, $^{2}J_{C-F}$ = 32.7 Hz, C-4'), 125.2 (2C, q, $^{3}J_{C-F}$ = 4.1 Hz, C-3', C-5'), 124.4 (1C, q, $^{1}J_{C-F}$ = 271.8 Hz, **C**F_3), 115.2 (C-3", C-5"), 35.1 (C-1), 34.4 (C-3), 32.9 (C-2) (Plate 39b and 39c). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -62.3 (s, CF_3) (Plate 39d).

40. Synthesis of 3-(3-(biphenyl-4-yl)propyl)phenol (117)

Compound (**117**) was synthesized according to the general procedure using (*E*)-1-(biphenyl-4-yl)-3-(3-hydroxyphenyl)prop-2-en-1-one (0.500 g; 1.67 mmol) as starting material.

The fraction R_f 0.52 yielded 3-(3-(biphenyl-4-yl)propyl)phenol (**117**) as a colourless oil (0.415 g, 86%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.61 – 7.23 (9H, m, H-2', H-3', H-5', H-6', H-8, H-9, H-10, H-11, H-12), 7.15 (1H, t, J = 7.8 Hz, H-5"), 6.80 – 6.64 (3H, m, H-2", H-4", H-6"), 2.70 – 2.67 (2H, m, H-1), 2.66 – 2.61 (2H, m, H-3), 2.02 – 1.94 (2H, m, H-2) (Plate 401a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.5 (C-3"), 144.3 (C-1"), 141.4 (C-1'), 141.1 (C-7), 138.8 (C-4'), 129.5 (C-10), 128.9 (C-9, C-11), 128.7 (C-8, C-12), 128.3 (C-5"), 127.1 (C-2', C-6'), 127.0 (C-3', C-5'), 121.1 (C-2"), 115.4 (C-4"), 112.7 (C-6"), 35.3 (C-1), 35.0 (C-3), 32.7 (C-2) (Plate 40b).

Synthesis of aminoalkylated diarylpropanes

A mixture of the appropriate diarylpropane (1 eq.), paraformaldehyde (1.5 eq.) and the appropriate amine (2 eq.) was dissolved in EtOH (2 mL) and conc. HCl (5 drops). The

reaction mixture was refluxed for 9 hours until TLC showed the disappearance of the starting material. The reaction mixture was quenched with solid $NaHCO_3$, extracted with EtOAc (2 x 50 mL) and washed with water (2 x 50 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure.

41. Synthesis of 5-(3-(4-methoxyphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (64)

Compound (**64**) was synthesized according to the general method using 3-(3-(4-methoxyphenyl)propyl)phenol (**63**) (0.165 g; 0.68 mmol), paraformaldehyde (0.037 g; 1.23 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by flash column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.52 yielded 5-(3-(4-methoxyphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**64)** as a light-yellow oil[166] (0.095 g, 41%). ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 7.10 (2H, d, J = 8.7 Hz, H-2', H-6'), 6.86 (1H, d, J = 7.2 Hz, H-5''), 6.82 (2H, d, J = 8.7 Hz, H-3', H-5'), 6.58 – 6.54 (1H, d, J = 1.5 Hz, H-2'', 1H, dd, J = 7.3, 1.5 Hz, H-6''), 3.73 (3H, s, OC**H$_3$**), 3.59 (2H, s, C**H$_2$**), 2.56 (2H, t, J = 7.6 Hz, H-1), 2.53 (2H, t, J = 7.6 Hz, H-3), 2.45 (4H, br s, H-2''', H-6'''), 1.91 – 1.82 (2H, m, H-2), 1.57 (4H, p, H-3''', H-5'''), 1.46 (2H, br s, H-4''') (Plate 41a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 159.0 (C-4'), 158.8 (C-3''), 143.7 (C-1''), 135.0 (C-1'), 130.1 (C-2', C-6'), 129.3 (C-5''), 120.0 (C-4''), 119.6 (C-6''), 116.4 (C-2''), 114.5 (C-3', C-5'), 62.3 (**C**H$_2$), 55.4 (C-2''', C-6'''), 54.4 (O**C**H$_3$), 35.8 (C-3), 35.2 (C-1), 34.2 (C-2), 26.7 (C-3''', C-5'''), 24.7 (C-4''') (Plate 41b).

IR (KBr): ν_{max} = 2932.41, 2360.34, 1510.49, 1242.60 cm^{-1}
Found (EI) M^+ 339.2198, $C_{22}H_{29}NO_2$ requires 339.2202.

42. Synthesis of 5-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (73)

Compound (**73**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by flash column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.51 yielded 5-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (**73**) as a

light-yellow oil (0.098 g, 67%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.17 (2H, d J = 6.3 Hz, H-3', H-5'), 7.13 – 7.05 (3H, m, H-2', H-4', H-6'), 6.76 (1H, d, J = 7.5 Hz, H-5''), 6.58 (1H, d, J = 1.5 Hz, H-2''), 6.50 (1H, dd, J = 7.5, 1.5 Hz, H-6''), 3.53 (2H, s, C**H$_2$**), 2.55 (2H, t, J = 7.5 Hz, H-1), 2.49 (2H, t, J = 7.5 Hz, H-3), 2.26 (4H, bs, H-2''', H-6'''), 1.89 – 1.80 (2H, m, H-2), 1.53 (6H, m, H-3''', H-4''', H-5''') (Plate 42a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3''), 143.1 (C-1''), 142.5 (C-1'), 129.1 (C-5''), 128.5 (C-3', C-5'), 128.3 (C-2', C-6'), 125.7 (C-4'), 125.4 (C-4''), 119.1 (C-6''), 116.1 (C-2''), 62.0 (**C**H$_2$), 53.9 (C-2''', C-6'''), 35.5 (C-3), 35.3 (C-1), 32.8 (C-2), 25.9 (C-3''', C-5'''), 24.1 (C-4''') (Plate 42b).

IR (neat): ν_{max} = 2937.48, 1427.05, 1116.77, 699.90 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 310.2091, ($C_{21}H_{27}NO + H^+$) requires *m/z* 310.2093.

43. Synthesis of 5-(3-(4-methoxyphenyl)propyl)-2,4-bis(piperidin-1-ylmethyl)phenol (65)

Compound (**65**) was synthesized according to the general procedure using 3-(3-(4-methoxyphenyl)propyl)phenol (**63**) (0.458 g; 1.89 mmol), paraformaldehyde (0.074 g; 2.47 mmol), and piperidine (0.25 mL; 2.50 mmol) as starting materials. The crude reaction mixture was separated by flash column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.48 yielded 5-(3-(4-methoxyphenyl)propyl)-2,4-bis(piperidin-1-ylmethyl)phenol (**65**) as a yellow oil (0.450 g, 55%). ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 7.15 (2H, d, J = 8.6 Hz, H-2', H-6'), 6.85 (1H, d, J = 8.6 Hz, H-3', H-5'), 6.79 (1H, s, H-5''), 6.55 (1H, s, H-2''), 3.76 (3H, s, OC**H$_3$**), 3.60 (2H, s, C**H$_2$**), 3.20 (2H, s, C**H$_2$**), 2.64 (2H, d, J = 7.4 Hz, H-1), 2.63 – 2.61 (2H, m, H-3), 2.55 - 2.18 (8H, H-2''', H-2'''', H-6''', H-6''''), 1.91 – 1.82 (2H, m, H-2), 1.62 – 1.53 (8H, H-3''', H-3'''', H-5''', H-5''''), 1.50 – 1.42 (4H, H-4''', H-4'''') (Plate 43a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 158.8 (C-4'), 158.0 (C-3''), 143.3 (C-1''), 135.3 (C-1'), 131.6 (C-5''), 130.1 (C-2', C-6'), 127.5 (C-4''), 119.3 (C-6''), 117.4 (C-2''), 114.5 (C-3', C-5'), 62.4 (**C**H$_2$), 61.9 (**C**H$_2$), 55.4 (O**C**H$_3$), 55.0 (2 x N-**C**), 54.4 (2 x N-**C**), 35.9 (C-1), 34.4 (C-3), 32.7 (C-2), 26.9 (2 x N-**C**), 26.7 (2 x N-**C**), 25.4 (1 x N-**C**), 24.8 (1 x N-**C**) (Plate 43b).
IR (neat): ν_{max} = 2930.49, 1511.28, 1243.80, 1037.40, 787.10 cm^{-1}
Found (TOF MS ES) $[M+H]^+$, 437.3169 ($C_{28}H_{40}N_2O_2 + H^+$) requires *m/z* 437.3168.
HPLC purity 90.8%, t_R = 1.47 min.

44. Synthesis of 2-(piperidin-1-ylmethyl)-4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (66)

Compound (**66**) was synthesized according to the general procedure using 4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (**116**) (0.050 g; 0.18 mmol), paraformaldehyde (0.052 g; 1.73 mmol), and piperidine (0.18 mL; 1.84 mmol) as starting materials. The crude reaction mixture was separated by flash column chromatography (H:EtOAc 6:4, 1.5 cm x 15 cm).

The fraction R_f 0.52 yielded 2-(piperidin-1-ylmethyl)-4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (**66**) as a yellow oil (0.058 g, 86%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.45 (2H, d, J = 8.0 Hz, H-3', H-5'), 7.20 (2H, d, J = 8.0 Hz, H-2', H-6'), 6.88 (1H, dd, J = 8.2, 2.2 Hz, H-6"), 6.67 (1H, d, J = 2.2 Hz, H-2"), 6.66 (1H, d, J = 8.2 Hz, H-5"), 3.55 (2H, s, C**H$_2$**), 3.16 – 2.02 (4H, H-2"', H-6"'), 2.63 – 2.56 (2H, m, H-1), 2.49 – 2.42 (2H, m, H-3), 1.90 – 1.75 (2H, m, H-2), 1.61 – 1.51 (4H, m, H-3"', H-5"'), 1.40 (2H, s, H-4"') (Plate 44a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 156.1 (C-3"), 146.6 (C-1"), 132.1 (C-1'), 128.7 (C-2'), 128.4 (C-6'), 128.3 (C-4"), 128.1 (1C, q, $^2J_{C-F}$ = 32.3 Hz, C-4'), 125.2 (2C, q, $^3J_{C-F}$ = 3.9 Hz, C-3', C-5'), 124.4 (1C, q, $^1J_{C-F}$ = 272.2 Hz, **C**F_3), 121.4 (C-6"), 115.8 (C-2", C-5"), 62.2 (**C**H_2), 53.9 (C-2"', C-6"'), 35.2 (C-3), 34.5 (C-1), 33.0 (C-2), 25.9 (C-3"', C-5"'), 24.0 (C-4"') (Plate 45b and 45c). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -118.1 (s, CF_3) (Plate 44d).

IR (neat): ν_{max} = 2936.14, 1497.96, 1323.65, 1116.64, 1067.03 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 378.2043, ($C_{22}H_{26}F_3NO + H^+$) requires m/z 378.2045.
HPLC purity 87.3%, t_R = 1.73 min.

45. Synthesis of 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (67)

Compound (**67**) was synthesized according to the general procedure using 3-(3-(4-fluorophenyl)propyl)phenol (**115**) (0.200 g; 0.87 mmol), paraformaldehyde (0.052 g; 1.73 mmol), and piperidine (0.18 mL; 1.84 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.50 yielded 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**67**) as a yellow oil (0.269 g, 95%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.05 (2H, dd, $^3J_{H-H}$

= 8.6 Hz; $^{4}J_{H\text{-}F}$ = 5.5 Hz, H-2', H-6'), 6.87 (2H, t, $^{3}J_{H\text{-}H}$ = 8.6 Hz; $^{4}J_{H\text{-}F}$ = 8.6 Hz, H-3', H-5'), 6.78 (1H, d, J = 7.6 Hz, H-5''), 6.57 (1H, d, J = 1.3 Hz, H-2''), 6.50 (1H, dd, J = 7.6, 1.3 Hz, H-6''), 3.55 (2H, s, C**H$_2$**), 2.55 – 2.51 (2H, m, H-3), 2.50 – 2.46 (2H, m, H-2), 2.41 – 2.04 (4H, H-2''', H-6'''), 1.87 – 1.78 (2H, m, H-2), 1.64 – 1.32 (6H, H-3''', H-4''', H-5''') (Plate 45a). ^{13}C APT NMR δ (150 MHz, $CDCl_3$, Me_4Si) 161.2 (1C, d, $^{1}J_{C\text{-}F}$ = 243.1 Hz, C-4'), 158.0 (C-3''), 142.8 (C-1''), 138.0 (1C, d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, C-1'), 129.7 (2C, d, $^{3}J_{C\text{-}F}$ = 7.7 Hz, C-2', C-6'), 128.3 (C-2''), 119.1 (C-4''), 119.0 (C-6''), 116.0 (C-2''), 115.0 (2C, d, $^{2}J_{C\text{-}F}$ = 20.9 Hz, C-3', C-5'), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 35.1 (C-3), 34.6 (C-1), 32.9 (C-2), 25.9 (C-3''', C-5'''), 24.0 (C-4''') (Plate 45b and 45c). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -118.1 (s, F) (Plate 45d).

IR (neat): ν_{max} = 2934.84, 1508.34, 1218.86, 819.83 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 328.2073, ($C_{21}H_{26}FNO + H^+$) requires *m/z* 328.2077.
HPLC purity 96.9%, t_R = 1.62 min.

46. Synthesis of 5-(3-(4-bromophenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (118)

Compound (**118**) was synthesized according to the general procedure using 3-(3-(4-bromophenyl)propyl)phenol (0.200 g; 0.87 mmol), paraformaldehyde (0.052 g; 1.73 mmol), and piperidine (0.18 mL; 1.84 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.53 yielded 5-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (**118**) as a yellow oil (0.215 g, 80%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.24 – 7.06 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.78 (1H, d, J = 7.6 Hz, H-5''), 6.59 (1H, d, J = 1.5 Hz, H-2''), 6.52 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.56 (2H, s, C**H$_2$**), 3.43 – 2.05 (4H, H-2''', H-6'''), 2.57 (2H, t, J = 7.7 Hz, H-1), 2.50 (2H, t, J = 7.7 Hz, H-3), 1.91 – 1.80 (2H, m, H-2), 1.62 – 1.30 (6H, m, H-3''', H-4''', H-5''') (Plate 46a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.9 (C-3''), 143.1 (C-1''), 142.4 (C-1'), 128.5 (C-2', C-6'), 128.4 (C-5''), 128.2 (C-3', C-5'), 125.7 (C-4''), 119.1 (C-6''), 119.0 (C-4'), 116.1 (C-2''), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 35.5 (C-3), 35.2 (C-1), 32.8 (C-2), 25.8 (C-3''', C-5'''), 24.0 (C-4''') (Plate 46b).

According to 1H NMR and MS Br is absent from the structure and correlates with the structure and NMR of (**73**). Br was removed during hydrogenation.

IR (neat): ν_{max} = 2918.55, 816.87, 752.37, 698.59 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 310.2215, ($C_{21}H_{27}NO + H^+$) requires *m/z* 310.2093.
HPLC purity 99.4%, t_R = 1.63 min.

47. Synthesis of 2-(piperidin-1-ylmethyl)-5-(3-*p*-tolylpropyl)phenol (68)

Compound (**68**) was synthesized according to the general procedure using 3-(3-*p*-tolylpropyl)phenol (**114**) (0.100 g; 0.44 mmol), paraformaldehyde (0.064 g; 2.13 mmol), and piperidine (0.18 mL; 1.84 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.55 yielded 2-(piperidin-1-ylmethyl)-5-(3-*p*-tolylpropyl)phenol (**68**) as a yellow oil (0.139 g, 98%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.01 (4H, s, H-2', H-3', H-5', H-6'), 6.78 (1H, d, J = 7.6 Hz, H-5''), 6.59 (1H, d, J = 1.3 Hz, H-2''), 6.51 (1H, dd, J = 7.6, 1.3 Hz, H-6''), 3.56 (2H, s, C**H$_2$**), 2.85 – 2.35 (4H, H-2''', H-6'''), 2.55 – 2.46 (4H, m, H-1, H-3), 2.24 (3H, s, C**H$_3$**), 1.84 (2H, m, H-2), 1.58 – 1.50 (6H, m, H-3''', H-4''', H-5''') (Plate 47a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.9 (C-3''), 143.1 (C-1'), 139.3 (C-1''), 135.1 (C-4'), 129.0 (C-2', C-6'), 128.3 (C-3', C-5'), 128.2 (C-5''), 119.1 (C-6''), 119.0 (C-4''), 116.0 (C-2''), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 35.2 (C-3), 35.0 (C-1), 32.8 (C-2), 25.7 (C-3''', C-5'''), 24.1 (C-4'''), 21.0 (**C**H_3) (Plate 47b).

IR (neat): ν_{max} = 2930.06, 2859.80, 1706.90, 1063.00 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 324.2325, ($C_{22}H_{29}NO + H^+$) requires *m/z* 324.2327.
HPLC purity 98.5%, t_R = 1.66 min.

48. Synthesis of 5-(3-(4-ethylphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (69)

Compound (**69**) was synthesized using 3-(3-(4-ethylphenyl)propyl)phenol (0.100 g; 0.42 mmol), paraformaldehyde (0.076 g; 2.53 mmol) and piperidine (0.10 mL; 1.00 mmol) according to the general procedure. The crude reaction mixture was chromatographed (TLC, T:A 7:3).
The fraction R_f 0.50 yielded 5-(3-(4-ethylphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**69**) as a yellow oil (0.087 g, 62%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.03 (4H, s, H-2', H-6', H-3', H-5'), 6.77 (1H, d, J = 7.6 Hz, H-5''), 6.58 (1H, d, J = 1.4 Hz, H-2''), 6.51 (1H, dd, J =

7.6, 1.4 Hz, H-6''), 3.54 (2H, s, C**H$_2$**), 2.57 – 2.29 (8H, m, H-1, H-3, 2 x N-C**H$_2$**), 2.26 – 2.02 (2H, m, CH_3-C**H$_2$**), 1.89 – 1.80 (2H, m, H-2), 1.58 – 1.51 (4H, m, 2 x N-C**H$_2$**), 1.38 (2H, br s, 1 x N-C**H$_2$**), 1.14 (3H, t, J = 7.6 Hz, C**H$_3$**) (Plate 48a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3''), 143.1 (C-4'), 141.5 (C-1''), 139.6 (C-1'), 128.4 (C-2', C-6'), 128.3 (C-5''), 127.8 (C-3', C-5'), 119.1 (C-6''), 119.0 (C-4''), 116.0 (C-2''), 62.0 (**C**H_2), 53.9 (C-2''', C-6'''), 35.2 (C-3), 35.0 (C-1), 32.8 (C-2), 28.5 (CH_3-**C**H_2), 25.9 (C-3''', C-5'''), 24.1 (C-4'''), 15.7 (**C**H_3) (Plate 48b).

IR (neat): ν_{max} = 2919.13, 1452.40, 1390.20, 782.72 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 338.2486, ($C_{23}H_{31}NO + H^+$) requires *m/z* 338.2484.
HPLC purity 99.4%, t_R = 1.75 min.

49. Synthesis of 2-(piperidin-1-ylmethyl)-5-(3-(thiophen-2-yl)propyl)phenol (70)

Compound (**70**) was synthesized according to the general procedure using 3-(3-(thiophen-2-yl)propyl)phenol (**113**) (0.100 g; 0.46 mmol), paraformaldehyde (0.035 g; 1.16 mmol), and piperidine (0.10 mL; 1.00 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 8:2).

The fraction R_f 0.53 yielded 2-(piperidin-1-ylmethyl)-5-(3-(thiophen-2-yl)propyl)phenol (**70**) as a colourless oil (0.130 g, 90%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.07 (1H, dd, J = 5.1, 1.1 Hz, H-4'), 6.87 (1H, dd, J = 5.1, 3.4 Hz, H-3'), 6.82 (1H, d, J = 7.6 Hz, H-5''), 6.77 – 6.72 (1H, m, H-2'), 6.62 (1H, d, J = 1.5 Hz, H-2''), 6.56 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.60 (2H, s, C**H$_2$**), 2.81 (2H, t, J = 7.5 Hz, H-1), 2.57 (2H, t, J = 7.5 Hz, H-3), 2.31 (4H, br s, H-2''', H-6'''), 1.95 (2H, p, J = 7.6 Hz, H-2), 1.59 (6H, br s, H3''', H-4''', H-5''') (Plate 49a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3''), 145.3 (C-1'), 142.7 (C-1''), 128.4 (C-5''), 126.7 (C-3'), 124.1 (C-2'), 122.9 (C-4'), 119.1 (C-6''), 116.1 (C-2''), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 34.9 (C-1), 33.1 (C-3), 29.4 (C-2), 25.8 (C-3''', C-5'''), 24.0 (C-4''') (Plate 49b).

IR (neat): ν_{max} = 2932.96, 1580.83, 1471.29, 1278.28, 989.29, 691.33 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 316.1732, ($C_{19}H_{25}NOS + H^+$) requires *m/z* 316.1735.

50. Synthesis of 5-(3-(biphenyl-4-yl)propyl)-2-(piperidin-1-ylmethyl)phenol (90)

Compound (**90**) was synthesized according to the general procedure using 3-(3-(biphenyl-4-yl)propyl)phenol (**117**) (0.120 g; 0.42 mmol), paraformaldehyde (0.025 g; 0.83 mmol), and piperidine (0.12 mL; 1.20 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.58 yielded 5-(3-(biphenyl-4-yl)propyl)-2-(piperidin-1-ylmethyl)phenol (**90**) as a yellowish oil (0.087 g, 54%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.61 – 7.57 (2H, m, H-8, H-12), 7.52 (2H, d, J = 8.2 Hz, H-2', H-6'), 7.43 (2H, t, J = 7.7 Hz, H-9, H-11), 7.35 – 7.31 (1H, m, H-10), 7.27 (2H, d, J = 8.2 Hz, H-3', H-5'), 6.87 (1H, d, J = 7.6 Hz, H-5''), 6.69 (1H, d, J = 1.5 Hz, H-2''), 6.62 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.64 (2H, s, C**H$_2$**), 2.69 (2H, t, J = 7.5 Hz, H-1), 2.62 (2H, t, J = 7.5 Hz, H-3), 2.18 (4H, bs, H-2''', H-6'''), 1.98 (2H, p, J = 7.7 Hz, H-2), 1.63 (6H, m, H3''', H-4''', H-5''') (Plate 50a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3''), 143.0 (C-1'), 141.6 (C-1''), 141.2 (C-7), 138.7 (C-4'), 128.9 (C-2', C-6'), 128.7 (C-3', C-5'), 128.3 (C-5''), 127.1 (C-8, C-12), 127.0 (C-9, C-11), 126.9 (C-10), 119.1 (C-4''), 119.0 (C-6''), 116.0 (C-2''), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 35.2 (C-1), 35.1 (C-3), 32.7 (C-2), 25.9 (C-3''', C-5'''), 24.1 (C-4''') (Plate 50b).

Found (TOF MS ES) $[M+H]^+$ 386.2485, ($C_{27}H_{31}NO + H^+$) requires *m/z* 386.2484.

51. Synthesis of 5-(3-(4-(isopropylamino)phenyl)propyl)-2-(piperidin-1-ylmethyl)-phenol (71)

Compound (**71**) was synthesized according to the general procedure using 3-(3-(4-(isopropylamino)phenyl)propyl)phenol (**92**) (0.050 g; 0.19 mmol), paraformaldehyde (0.012 g; 0.40 mmol), and piperidine (0.09 mL; 0.93 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.52 yielded 5-(3-(4-(isopropylamino)phenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**71**) as a light-yellow oil (0.059 g, 85%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 6.94 (2H, d, J = 8.5 Hz, H-2', H-6'), 6.79 (1H, d, J = 7.6 Hz, H-5''), 6.61 (1H, d, J = 1.5 Hz, H-2''), 6.54 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 6.48 (2H, d, J = 8.5 Hz, H-3', H-5'), 3.57

(2H, s, C**H$_2$**), 3.54 (1H, p, J = 6.3 Hz, -NH-C**H**-), 3.34 – 1.91 (4H, H-2''', H-6'''), 2.53 – 2.45 (4H, m, H-1, H-3), 1.89 – 1.76 (2H, m, H-2), 1.62 – 1.28 (6H, m, H-3''', H-4''', H-5'''), 1.15 (C**H$_3$**), 1.14 (C**H$_3$**) (Plate 51a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.9 (C-3''), 145.5 (C-4'), 143.4 (C-1''), 130.9 (C-1'), 129.2 (C-2', C-6'), 128.3 (C-5''), 119.1 (C-6''), 118.9 (C-4''), 116.0 (C-2''), 113.4 (C-3', C-5'), 62.0 (**C**H$_2$), 53.9 (C-2''', C-6'''), 45.5 (-NH-**C**H-), 35.2 (C-1), 34.5 (C-3), 33.1 (C-2), 25.9 (C-3''', C-5'''), 24.1 (C-4''') 23.1 (2 x **C**H$_3$) (Plate 51b).

IR (neat): ν_{max} = 2932.30, 1615.34, 1516.20, 812.18, 783.32 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 367.2760, ($C_{24}H_{34}N_2O + H^+$) requires *m/z* 367.2749.
HPLC purity 99.1%, t_R = 1.52 min.

52. Synthesis of 4-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (72)

Compound (**72**) was synthesized according to the general procedure using 4-(3-phenylpropyl)phenol (0.050 g; 0.24 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and piperidine (0.09 mL; 0.93 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 8:2).

The fraction R_f 0.50 yielded 4-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (**72**) as a colourless oil (0.072 g, 97%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.22 – 7.17 (2H, m, H-2', H-6'), 7.13 – 7.07 (3H, H-3', H-4', H-5'), 6.89 (1H, dd, J = 8.2, 1.8 Hz, H-6''), 6.68 (1H, d, J = 1.8 Hz, H-2''), 6.66 (1H, d, J = 8.2 Hz, H-5''), 3.55 (3H, s, C**H$_2$**), 2.56 (2H, t, J = 7.7 Hz, H-1), 2.46 (2H, t, J = 7.7 Hz, H-3), 1.87 – 1.77 (2H, m, H-2), 1.67 – 1.14 (10H, br s, H-2''', H-3''', H-4''', H-5''', H-6''') (Plate 52a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 156.0 (C-4''), 142.5 (C-1'), 132.5 (C-1''), 128.5 (C-2', C-6'), 128.4 (C-2''), 128.3 (C-6''), 128.2 (C-3', C-5'), 125.7 (C-4'), 121.4 (C-3''), 115.7 (C-5''), 62.3 (**C**H$_2$), 53.9 (C-2''', C-6'''), 35.5 (C-3), 34.6 (C-1), 33.3 (C-2), 25.9 (C-3''', C-5'''), 24.0 (C-4''') (Plate 52b).

IR (neat): ν_{max} = 2937.48, 1427.05, 1116.77, 699.90 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 310.2090, ($C_{21}H_{27}NO + H^+$) requires *m/z* 310.2093.

53. Synthesis of 5-(3-phenylpropyl)-2-(piperazin-1-ylmethyl)phenol (74)

Compound (**74**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and piperazine (0.074 g; 0.86 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 8:2).

The fraction R_f 0.51 yielded 5-(3-phenylpropyl)-2-(piperazin-1-ylmethyl)phenol (**74**) as a yellow oil (0.098 g, 67%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.24 – 7.08 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.80 (1H, d, J = 7.6 Hz, H-5''), 6.59 (1H, d, J = 1.5 Hz, H-2''), 6.53 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.60 (3H, s, C**H$_2$**), 2.69 (8H, br s, H-2''', H-3''', H-5''', H-6'''), 2.57 (2H, t, J = 7.5 Hz, H-1), 2.51 (2H, t, J = 7.5 Hz, H-3), 1.87 (2H, p, J = 7.7 Hz, H-2) (Plate 53a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.6 (C-3''), 143.3 (C-1'), 142.4 (C-1''), 128.5 (C-3', C-5'), 128.4 (C-2', C-6'), 128.3 (C-5''), 125.7 (C-4'), 119.3 (C-4''), 118.6 (C-6''), 116.1 (C-2''), 61.2 (**C**H_2), 52.5 (C-1), 51.3 (C-3), 35.5 (C-2''', C-6'''), 35.2 (C-3''', C-5'''), 32.8 (C-2) (Plate 53b).

IR (neat): ν_{max} = 2933.16, 2819.67, 1269.44, 1002.68, 697.71 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 311.2212, ($C_{20}H_{26}N_2O + H^+$) requires *m/z* 311.2214.

54. Synthesis of 2-((4-methylpiperazin-1-yl)methyl)-5-(3-phenylpropyl)phenol (75)

Compound (**75**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and 1-methylpiperazine (0.15 mL; 1.35 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 8:2).

The fraction R_f 0.50 yielded 5-(3-phenylpropyl)-2-(piperazin-1-ylmethyl)phenol (**75**) as a yellow oil (0.098 g, 64%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.23 – 7.08 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.81 (1H, d, J = 7.6 Hz, H-5''), 6.60 (1H, d, J = 1.5 Hz, H-2''), 6.54 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.61 (3H, s, C**H$_2$**), 3.15 – 2.05 (8H, m, H-2''', H-3''', H-5''', H-6'''), 2.57 (2H, t, J = 7.7 Hz, H-1), 2.51 (2H, t, J = 7.7 Hz, H-3), 2.23 (3H, s, C**H$_3$**), 1.91 – 1.82 (2H, m, H-2) (Plate 54a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.6 (C-3''), 143.4 (C-1'), 142.4 (C-1''), 128.5 (C-5''), 128.4 (C-2', C-6'), 128.3 (C-3', C-5'), 125.7 (C-4'), 119.3 (C-6''),

118.5 (C-4''), 116.0 (C-2''), 61.1 (**C**H_2), 55.0 (C-2''', C-5'''), 52.5 (C-3''', C-4'''), 45.9 (C-3), 35.4 (C-1), 35.2 (C-2), 32.8 (**C**H_3) (Plate 54b).

IR (neat): ν_{max} = 2935.06, 2793.77, 1452.32, 1160.99, 698.42 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 325.2282, ($C_{21}H_{28}N_2O + H^+$) requires *m/z* 325.2280.
HPLC purity 99.9%, t_R = 1.57 min.

55. Synthesis of 2-((4-ethylpiperazin-1-yl)methyl)-5-(3-phenylpropyl)phenol (76)

Compound (**76**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and 1-ethylpiperazine (0.15 mL; 1.18 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.55 yielded 2-((4-ethylpiperazin-1-yl)methyl)-5-(3-phenylpropyl)phenol (**76**) as a yellow oil (0.109 g, 69%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.24 – 7.06 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.80 (1H, d, J = 7.6 Hz, H-5''), 6.59 (1H, d, J = 1.5 Hz, H-2''), 6.53 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.60 (3H, s, C**H**$_2$), 2.74 (8H, br s, H-2''', H-3''', H-5''', H-6'''), 2.57 (2H, t, J = 7.5 Hz, H-1), 2.50 (2H, t, J = 7.5 Hz, H-3), 2.35 (2H, q, J = 7.2 Hz, -N-C**H**$_2$-CH_3), 1.86 (2H, p, J = 7.7 Hz, H-2), 1.01 (3H, t, J = 7.2 Hz, C**H**$_3$) (Plate 55a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.6 (C-3''), 143.3 (C-1'), 142.4 (C-1''), 128.5 (C-5''), 128.4 (C-3', C-5'), 128.3 (C-2', C-6'), 125.7 (C-4'), 119.3 (C-4''), 118.6 (C-6''), 116.0 (C-2''), 61.2 (**C**H_2), 52.6 (C-3''', C-5'''), 52.5 (C-2''', C-6'''), 52.2 (-N-**C**H_2-CH_3), 35.5 (C-1), 35.2 (C-3), 32.8 (C-2), 12.0 (**C**H_3) (Plate 55b).

IR (neat): ν_{max} = 2815.82, 1451.07, 1160.59, 731.17, 698.23 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 339.2433, ($C_{22}H_{30}N_2O + H^+$) requires *m/z* 339.2436.

56. Synthesis of 5-(3-phenylpropyl)-2-(pyrrolidin-1-ylmethyl)phenol (77)

Compound (**77**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and pyrrolidine (0.10 mL; 1.22 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.50 yielded 5-(3-phenylpropyl)-2-(pyrrolidin-1-ylmethyl)phenol (**77**) as a yellow oil (0.092 g, 66%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.23 – 7.08 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.80 (1H, d, J = 7.6 Hz, H-5''), 6.59 (1H, d, J = 1.5 Hz, H-2''), 6.52 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.71 (3H, s, C**H$_2$**), 2.59 – 2.47 (8H, H-1, H-3, H-2''', H-5'''), 2.90 – 2.83 (2H, m, H-2), 1.78 – 1.73 (4H, m, H-3''', H-4''') (Plate 56a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.9 (C-3''), 143.0 (C-1'), 142.4 (C-1''), 128.5 (C-3', C-5'), 128.3 (C-2', C-6'), 127.7 (C-5''), 125.7 (C-4'), 119.9 (C-4''), 119.0 (C-6''), 115.9 (C-2''), 58.6 (**C**H$_2$), 53.5 (C-3''', C-5'''), 35.5 (C-2''', C-6'''), 35.2 (-N-**C**H$_2$-CH$_3$), 32.8 (C-1), 23.7 (C-3), (C-2), (**C**H$_3$) (Plate 56b).

IR (neat): ν_{max} = 2932.23, 1454.11, 1273.86, 746.13, 698.03 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 296.2013, ($C_{20}H_{25}NO + H^+$) requires *m/z* 296.2014.

57. Synthesis of 2-(morpholinomethyl)-5-(3-phenylpropyl)phenol (78)

Compound (**78**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and morpholine (0.10 mL; 1.16 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.55 yielded 2-(morpholinomethyl)-5-(3-phenylpropyl)phenol (**78**) as a light brown oil (0.119 g, 81%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.30 – 7.19 (5H, m, H-2', H-3', H-4', H-5', H-6'), 6.91 (1H, d, J = 7.6 Hz, H-5''), 6.70 (1H, d, J = 1.5 Hz, H-2''), 6.64 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.70 (2H, s, C**H$_2$**), 2.71 – 2.38 (8H, m, H-2''', H-3''', H-5''', H-6'''), 2.66 (2H, t, J = 7.5 Hz, H-3), 2.60 (2H, t, J = 7.5 Hz, H-1), 1.99 – 1.93 (2H, m, H-2) (Plate 57a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.3 (C-3''), 142.3 (C-1''), 129.5 (C-1'), 128.7 (C-5''), 128.5 (C-3', C-5'), 128.3 (C-2', C-6'), 125.7 (C-4'), 119.5 (C-6''), 118.0 (C-4''), 116.1 (C-2''), 66.8 (C-5''', C-3'''), 61.6 (**C**H$_2$), 52.9 (C-2''', C-6'''), 35.4 (C-1), 35.2 (C-3), 32.8 (C-2) (Plate 57b).

IR (neat): ν_{max} = 2821.35, 1452.77, 1115.77, 863.96, 697.66 cm^{-1}
Found (TOF MS ES) 334.1785, ($C_{20}H_{25}NO_2$ + Na) requires *m/z* 334.1783.

58. Synthesis of 2-((dimethylamino)methyl)-5-(3-phenylpropyl)phenol (79)

Compound (**79**) was synthesized according to the general procedure using 3-(3-phenylpropyl)phenol (**112**) (0.100 g; 0.47 mmol), paraformaldehyde (0.028 g; 0.93 mmol), and dimethylamine (0.10 mL; 1.47 mmol) as starting materials. The crude reaction mixture was chromatographed (TLC, T:A 7:3).

The fraction R_f 0.51 yielded 2-((dimethylamino)methyl)-5-(3-phenylpropyl)phenol (**79**) as a light brown oil (0.102 g, 79%). ^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 7.16 (3H, t, J = 7.5 Hz, H-3', H-5'), 7.09 – 7.03 (3H, m, H-2', H-4', H-6'), 6.82 (1H, d, J = 7.6 Hz, H-5''), 6.47 – 6.42 (2H, m, H-2'', H-6''), 3.39 (2H, s, C**H$_2$**), 2.45 (2H, t, J = 7.7 Hz, H-1), 2.37 (2H, t, J = 7.7 Hz, H-3), 2.08 (6H, s, 2 x C**H$_3$**), 1.71 (2H, p, J = 7.7 Hz, H-2) (Plate 58a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 157.4 (C-3''), 142.6 (C-1'), 142.4 (C-1''), 129.3 (C-4'), 128.8 (C-2', C-6'), 128.7 (C-3', C-5'), 126.2 (C-5''), 120.5 (C-6''), 119.2 (C-4''), 115.6 (C-2''), 60.8 (**C**H$_2$), 44.6 (2 x **C**H$_3$), 35.2 (C-3), 34.9 (C-1), 33.0 (C-2) (Plate 58b).

IR (neat): ν_{max} = 2933.91, 2855.66, 1453.55, 1016.20, 847.27, 698.10 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 270.1855, ($C_{18}H_{23}NO + H^+$) requires *m/z* 270.1858.
HPLC purity 99.6%, t_R = 1.57 min.

General synthesis of HCl salts of the aminoalkylated diarylpropanes

At 0 °C the appropriate aminoalkylated diarylpropane was dissolved in dry DCM (10 mL). HCl gas was bubbled through the reaction mixture for 60 min. A small quantity of precipitation indicated the formation of the salt. The excess solvent was removed under N_2 gas and the product was freeze dried over night.

59. Synthesis of 1-(2-hydroxy-4-(3-(4-methoxyphenyl)propyl)benzyl)piperidinium chloride (80)

Compound (**80**) was synthesized according to the general procedure using 5-(3-(4-methoxyphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**64**) (0.200 g, 0.59 mmol) as starting material. 1-(2-hydroxy-4-(3-(4-methoxyphenyl)propyl)benzyl)piperidinium chloride (**80**) was obtained as a white solid (0.185 g, 84%).

^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 7.47 (1H, d, J = 7.8 Hz, H-5''), 7.13 (2H, d, J = 8.6 Hz, H-2', H-6'), 6.98 (1H, d, J = 1.2 Hz, H-2''), 6.84 (2H, d, J = 8.6 Hz, H-3', H-5'), 6.76 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 4.18 (2H, d, J = 4.7 Hz, C**H$_2$**), 3.76 (3H, s, OC**H$_3$**), 3.42 (2H, d, J = 11.6 Hz, H-2'''), 2.96 – 2.87 (6H, m, H-3''', H-4''', H-5'''), 2.63 – 2.53 (4H, m, H-1, H-3), 1.94 – 1.85 (2H, m, H-2''', H-6'''), 1.82 (2H, d, J = 14.5 Hz, H-6''') (Plate 59a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 158.9 (C-4'), 157.8 (C-3''), 147.0 (C-1''), 134.9 (C-1'), 134.7 (C-2', C-6'), 130.1 (C-5''), 121.3 (C-6''), 119.3 (C-4''), 115.7 (C-2''), 114.5 (C-3', C-5'), 55.4 (C-2''', C-6'''), 52.7 (O**C**H$_3$, **C**H$_2$), 35.8 (C-3), 35.1 (C-1), 34.0 (C-2), 23.5 (C-3''', C-5'''), 22.7 (C-4''') (Plate 59b).

IR (neat): ν_{max} = 2935.94, 1511.06, 1242.36, 1033.16, 827.06 cm^{-1}
Found (TOF MS ES) $[M+H]^+$, 340.2270 ($C_{22}H_{29}NO_2 + H^+$) requires *m/z* 340.2277.
HPLC purity 86.7%, t_R = 1.61 min.

60. Synthesis of 1-(2-hydroxy-4-(3-phenylpropyl)benzyl)piperidinium chloride (82)

Compound (**82**) was synthesized according to the general procedure using 5-(3-phenylpropyl)-2-(piperidin-1-ylmethyl)phenol (**73**) (0.200 g, 0.65 mmol) as starting material. 1-(2-hydroxy-4-(3-phenylpropyl)benzyl)piperidinium chloride (**82**) was obtained as a white solid (0.218 g, 97%).

^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.25 – 6.62 (8H, H-2', H-6', H-3', H-5', H-4', H-2'', H-5'', H-6''), 4.12 (2H, d, J = 3.6 Hz, C**H$_2$**), 3.50 – 1.15 (10H, H-2''', H-3''', H-4''', H-5''', H-6'''), 2.58 (2H, t, J = 7.8 Hz, H-1), 2.53 (2H, t, J = 7.8 Hz, H-3), 1.90 – 1.82 (2H, m, H-2) (Plate 60a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 156.9 (C-3''), 147.00 (C-1''), 142.1 (C-1'), 133.1 (Ar-**C**), 128.4 (C-2', C-6'), 128.3 (C-3', C-5'), 125.8 (Ar-**C**), 120.5 (Ar-**C**), 117.9 (Ar-**C**), 111.8 (Ar-**C**), 55.0 (**C**H$_2$), 51.7 (C-2''', C-6'''), 35.5 (C-3), 35.3 (C-1), 32.7 (C-2), 22.9 (C-3''', C-5'''), 21.7 (C-4''') (Plate 60b).

IR (neat): ν_{max} = 2937.48, 1427.05, 1116.77, 699.90 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 310.2174, ($C_{21}H_{27}NO + H^+$) requires *m/z* 310.2171.
HPLC purity 92.3%, t_R = 1.62 min.

61. Synthesis of 1-(4-(3-(4-fluorophenyl)propyl)-2-hydroxybenzyl)piperidinium chloride (81)

Compound (**81**) was synthesized according to the general procedure using 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**67**) (0.200 g, 0.61 mmol) as starting material. 1-(4-(3-(4-fluorophenyl)propyl)-2-hydroxybenzyl)piperidinium chloride (**81**) was obtained as a white solid (0.206 g, 93%).

^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.06 (2H, dd, $^{3}J_{H-H}$ = 8.6 Hz; $^{4}J_{H-F}$ = 5.5 Hz, H-2', H-6'), 7.04 (1H, d, J = 5.5 Hz, H-2''), 7.02 (1H, d, J = 7.7 Hz, H-5''), 6.88 (2H, t, $^{3}J_{H-H}$ = 8.6 Hz; $^{4}J_{H-F}$ = 8.6 Hz, H-3', H-5'), 6.63 (1H, dd, J = 7.7, 1.4 Hz, H-6''), 4.14 (2H, s, C**H$_2$**), 3.50 – 0.80 (10H, m, H-2''', H-3''', H-4''', H-5''', H-6'''), 2.54 (2H, t, J = 7.8 Hz, H-1), 2.50 (2H, t, J = 7.8 Hz, H-3), 1.82 (2H, p, J = 7.8 Hz, H-2) (Plate 61a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 161.2 (1C, d, $^{1}J_{C-F}$ = 243.2 Hz, C-4'), 156.8 (C-3''), 146.8 (C-1''), 137.6 (1C, d, $^{4}J_{C-F}$ = 3.2 Hz, C-1'), 133.0 (C-5''), 129.7 (2C, d, $^{3}J_{C-F}$ = 7.8 Hz, C-2', C-6'), 120.5 (C-6''), 118.2 (C-4''), 115.0 (2C, d, $^{2}J_{C-F}$ = 21.0 Hz, C-3', C-5'), 111.9 (C-2''), 55.0 (**C**H_2), 51.7 (C-2''', C-6'''), 35.1 (C-3), 34.7 (C-1), 32.8 (C-2), 22.9 (C-3''', C-5'''), 21.7 (C-4''') (Plate 61b and 61c). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -117.9 (s, F) (Plate 61d).

IR (neat): ν_{max} = 2937.54, 1508.12, 1427.41, 1217.12, 772.15 cm^{-1}
Found (TOF MS ES) $[M+H]^+$, 328.2075, ($C_{21}H_{26}FNO + H^+$) requires *m/z* 328.2077.

62. Synthesis of 1-(2-hydroxy-5-(3-(4-(trifluoromethyl)phenyl)propyl)benzyl)piperidinium chloride (83)

Compound (**83**) was synthesized according to the general procedure using 2-(piperidin-1-ylmethyl)-4-(3-(4-(trifluoromethyl)phenyl)propyl)phenol (**66**) (0.200 g, 0.53 mmol) as starting material. 1-(2-hydroxy-4-(3-(4-(trifluoromethyl)phenyl)propyl)benzyl)piperidinium chloride (**83**) was obtained as a white solid (0.195 g, 89%).

^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.45 (2H, d, J = 8.0 Hz, H-3', H-5'), 7.20 (2H, d, J = 7.8 Hz, H-2', H-6'), 7.11 (1H, d, J = 8.3 Hz, H-5''), 7.04 (1H, dd, J = 8.3, 1.5 Hz, H-6''), 6.90 (1H, d, J = 1.5 Hz, H-2''), 4.11 (2H, d, J = 3.7 Hz, C**H$_2$**), 3.46 (2H, d, J = 11.5 Hz, H-2), 2.63 – 2.58 (4H, H-1, H-3), 2.51 – 2.47 (2H, m, H-4'''), 2.15 – 1.69 (8H, m, H-2''', H-3''', H-5''', H-6''') (Plate 62a). ^{19}F NMR δ (282.4 MHz, $CDCl_3$, C_6F_6) -62.3 (s, CF_3) (Plate 62b).

Found (TOF MS ES) $[M+H]^+$, 378.2068, ($C_{22}H_{26}F_3NO + H^+$) requires *m/z* 378.2070.

63. Synthesis of 1-(4-(3-(4-ethylphenyl)propyl)-2-hydroxybenzyl)piperidinium chloride (84)

Compound (**84**) was synthesized according to the general procedure using 5-(3-(4-ethylphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**69**) (0.200 g, 0.59 mmol) as starting material. 1-(4-(3-(4-ethylphenyl)propyl)-2-hydroxybenzyl)piperidinium chloride (**84**) was obtained as a white solid (0.215 g, 98%).

^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.07 – 6.94 (6H, H-2', H-3', H-5', H-6', H-2", H-6"), 6.66 (1H, d, J = 7.7 Hz, H-5"), 4.11 (2H, s, C**H$_2$**), 3.47 (2H, d, J = 11.7 Hz, H-2), 2.65 – 1.50 (16H, H-2"', H-3"', H-4"', H-5"', H-6"', H-1, H-3, -C**H$_2$**CH_3), 1.15 (3H, t, J = 7.5 Hz, C**H$_3$**) (Plate 63).

Found (TOF MS ES) $[M+H]^+$, 338.1966, ($C_{23}H_{31}NO + H^+$) requires *m/z* 338.1968.

64. Synthesis of 2-(piperidin-1-ylmethyl)-5-(3-(4-propylphenyl)propyl)phenol (99)

Compound (**99**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3-(3-(4-propylphenyl)propyl)phenol (0.100 g; 0.39 mmol), paraformaldehyde (0.025 g; 0.83 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (T:A 8:2).

The fraction R_f 0.56 yielded 2-(piperidin-1-ylmethyl)-5-(3-(4-propylphenyl)propyl)phenol (**99**) as a light yellow oil (0.099 g, 72%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.33 – 6.90 (7H, H-2', H-3', H-5', H-6', H-2", H-5", H-6"), 3.44 (2H, s, C**H$_2$**), 3.17 – 1.52 (20H, H-1, H-2, H-3, H-4, H-5, H-2"', H-3"', H-4"', H-5"', H-6"'), 1.47 – 1.36 (3H, m, C**H$_3$**) (Plate 64a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 162.0 (C-3"), 160.4 (C-1"), 154.8 (C-4'), 150.2 (C-1'), 130.8 (C-5"), 129.8 (C-2', C-6'), 129.7 (C-3', C-5'), 122.7 (C-6"'), 115.1 (C-4"), 114.9 (C-2"), 57.9 (**C**H_2), 54.4 (C-2"', C-6"'), 36.8 (C-6), 36.5 (C-2), 34.8 (C-1, C-3), 34.6 (C-3"', C-5"'), 32.8 (C-5), 25.9 (C-4"'), 24.3 (**C**H_3) (Plate 64b).
IR (neat): ν_{max} = 2920.13, 1452.40, 1420.25, 1390.20,1365.34, 782.72 cm^{-1}
Found (TOF MS ES) 374.2550, ($C_{24}H_{33}NO$ + Na) requires *m/z* 374.2552.

65. Synthesis of 5-(3-(4-butylphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (100)

Compound (**100**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3-(3-(4-butylphenyl)propyl)phenol (0.050 g; 0.19 mmol), paraformaldehyde (0.010 g; 0.33 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (T:A 8:2).

The fraction R_f 0.52 yielded 5-(3-(4-butylphenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**100**) as a light yellow oil (0.065 g, 94%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.12 (4H, s, H-2', H-3', H-5', H-6'), 7.00 (1H, dd, J = 8.2, 1.2 Hz, H-6"), 6.79 (1H, d, J = 1.2 Hz, H-2"), 6.76 (1H, d, J = 8.2 Hz, H-5"), 3.66 (2H, s, C**H$_2$**), 2.66 – 1.28 (22H, H-1, H-2, H-3, H-4, H-5, H-6, H-2'", H-3'", H-4'", H-5'", H-6'"), 0.96 (3H, t, J = 7.5 Hz, C**H$_3$**) (Plate 65a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.9 (C-3"), 140.2 (C-1"), 139.6 (C-4'), 132.7 (C-1'), 128.4 (C-5"), 128.3 (C-2', C-6'), 128.2 (C-3', C-5'), 121.3 (C-6"), 115.7 (C-4", C-2"), 62.3 (**C**H$_2$), 53.9 (C-2'", C-6'"), 35.3 (C-1), 35.1 (C-3), 34.7 (C-4), 33.8 (C-5), 33.4 (C-2), 25.9 (C-3'", C-5'"), 24.1 (C-4'"), 22.4 (C-6), 14.0 (C-7) (Plate 65b).

IR (neat): ν_{max} = 2902.31, 1428.10, 1420.25,1398.01, 1390.20,1365.34, 782.72 cm^{-1}
Found (TOF MS ES) 388.5512, ($C_{25}H_{35}NO$ + Na) requires *m/z* 388.5515.

66. Synthesis of 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenyl 4-methylbenzenesulfonate (94)

Compound (**94**) was synthesized by dissolving 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenol (**67**) (0.030 g; 0.092 mmol) in dry DCM (5 mL) together with *p*-TSACl (30 mg). The reaction mixture was left to stir at room temperature overnight. The reaction was monitored by TLC and the reaction mixture was filtered through silica gel. The filtrate was dissolved in EtOAc followed by extraction with EtOAc (2 x 50 mL). The organic layer was washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting crude mixture was separated by column chromatography (H:EtOAc 7:3).

The fraction R_f 0.55 yielded 5-(3-(4-fluorophenyl)propyl)-2-(piperidin-1-ylmethyl)phenyl 4-methylbenzenesulfonate (**94**) as a light yellow oil (0.044 g, 99%). ^{1}H NMR δ (600 MHz,

$CDCl_3$, Me_4Si) 7.67 (2H, d, J = 8.3 Hz, 2 x H on S-ring), 7.31 (1H, d, J = 7.8 Hz, H-5"), 7.22 (2H, d, J = 8.0 Hz, 2 x H on S-ring), 7.04 (2H, dd, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 5.4 Hz, H-2', H-6'), 6.96 (1H, dd, J = 7.8, 1.5 Hz, H-6"), 6.90 (2H, t, $^3J_{H-H}$ = 8.6 Hz; $^4J_{H-F}$ = 8.6 Hz, H-3', H-5'), 6.75 (1H, d, J = 1.5 Hz, H-2"), 3.19 (2H, s, C**H$_2$**), 2.52 – 2.44 (4H, m, H-1, H-3), 2.35 (3H, s, C**H$_3$**), 2.23 – 2.08 (6H, H-3'", H-4'", H-5'"), 1.80 – 1.70 (2H, m, H-2), 1.48 – 1.42 (4H, m, H-2'", H-6'") (Plate 66a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 161.3 (1C, d, $^1J_{C-F}$ = 243.2 Hz, C-4'), 148.1 (C-3"), 145.3 (C-1"), 142.2 (1 x C on S-ring), 137.6 (1C, d, $^4J_{C-F}$ = 3.2 Hz, C-1'), 133.1 (1 x C on S-ring), 130.8 (C-5"), 129.8 (2 x C on S-ring), 129.7 (2C, d, $^3J_{C-F}$ = 7.8 Hz, C-2', C-6'), 128.5 (2 x C on S-ring), 127.1 (C-4"), 122.0 (C-2"), 115.1 (2C, d, $^2J_{C-F}$ = 21.0 Hz, C-3', C-5'), 56.5 (**C**H_2), 54.4 (C-2'", C-6'"), 34.6 (C-3), 34.4 (C-1), 32.7 (C-2), 31.0 (impurity), 25.9 (C-3'", C-5'"), 24.2 (C-4'"), 21.7 (**C**H_3) (Plate 66b and 66c).

IR (neat): ν_{max} = 2933.05, 1508.74, 1177.61, 790.00, 662.52 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 482.2177, ($C_{28}H_{32}FNO_3S + H^+$) requires *m/z* 482.2165.
HPLC purity 99.6%, t_R = 1.99 min.

67. Synthesis of 3,3'-(3,3'-(1,4-phenylene)bis(propane-3,1-diyl))diphenol (119)

Compound (**119**) was synthesized by dissolving (2*E*,2'*E*)-1,1'-(1,4-phenylene)bis(3-(3-hydroxyphenyl)prop-2-en-1-one) (0.100 g; 0.27 mmol) in a solution of EtOAc:H_2O (3:1 v/v) with $Pd(OH)_2/C$ (0.060 g). The reaction mixture was allowed to stir at room temperature under H_2 at atmospheric pressure. The reaction was monitored by TLC and filtered through silica gel. The filtrate was dissolved in EtOAc followed by extraction with EtOAc (2 x 50 mL). The organic layer was washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 3,3'-(3,3'-(1,4-phenylene)bis(propane-3,1-diyl))diphenol (**119**) as a light yellow oil (0.084 g, 90%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.07 (2H, t, J = 7.5 Hz, H-5", H-14'), 7.03 – 7.00 (4H, m, H-2', H-3', H-5', H-6'), 6.68 (2H, d, J = 7.7 Hz, H-6", H-15'), 6.60 – 6.56 (4H, m, H-2", H-4", H-11', H-13'), 2.53 (8H, m, H-1, H-3, H-7', H-9'), 1.85 (4H, m H-2, H-8') (Plate 67a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.6 (C-3", C-12'), 144.4 (C-1", C10'), 139.6 (C-1', C-4'), 129.5 (C-5", C-14'), 128.4 (C-2', C-3', C-5'), 128.3 (C-6'), 120.9 (C-6", C-15'), 115.4 (C-2", C-11"), 112.7 (C-4", C-13'), 35.3 (C-1, C-7'), 35.0

(C-3, C-9'), 32.8 (C-2, C-8') (Plate 67b).

68. Synthesis of 5,5'-(3,3'-(1,4-phenylene)bis(propane-3,1-diyl))bis(2-(piperidin-1-ylmethyl)phenol) (93)

Compound (**93**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3,3'-(3,3'-(1,4-phenylene)bis(propane-3,1-diyl))diphenol (**119**) (0.050 g; 0.14 mmol), paraformaldehyde (0.086 g; 2.87 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture separated by column chromatography (T:A 8:2, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 5,5'-(3,3'-(1,4-phenylene)bis(propane-3,1-diyl))bis(2-(piperidin-1-ylmethyl)phenol) (**93**) as a light brown oil (0.048 g, 63%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.03 (4H, s, H-2', H-3', H-5', H-6'), 6.79 (2H, d, J = 7.6 Hz, H-5", H-14'), 6.60 (2H, d, J = 1.5 Hz, H-2", H-11'), 6.53 (2H, dd, J = 7.6, 1.5 Hz, H-6", H-15'), 3.56 (4H, s, 2 x C**H$_2$**), 3.22 – 2.02 (8H, H-2'", H-6'", H-16', H-20'), 2.55 (4H, t, J = 7.7 Hz, H-1, H-7'), 2.51 (4H, t, J = 7.7 Hz, H-3, H-9'), 1.89 – 1.80 (4H, m, H-2, H-8'), 1.59 – 1.27 (12H, brbr s, H-3'", H-4'", H-5'", H-17', H-18', H-19') (Plate 68a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 157.9 (C-3", C-12'), 143.1 (C-1", C-10'), 139.7 (C-1', C-4'), 128.3 (C-2', C-3', C-5', C-6'), 128.2 (C-5", C-14'), 119.0 (C-6", C-15'), 118.9 (C-4", C-13'), 116.0 (C-2", C-11'), 61.9 (2 x **C**H$_2$), 53.9 (C-2'", C-6'", C-16', C-20'), 35.2 (C-1, C-7'), 35.0 (C-3, C-9'), 32.8 (C-2, C-8'), 25.9 (C-3'", C-5'", C-17', C-19'), 24.1 (C-4'", C-18') (Plate 68b).
IR (neat): ν_{max} = 2932.41, 1441.94, 1277.29, 1068.24, 988.81, 746.39 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 541.3793, ($C_{36}H_{48}N_2O_2 + H^+$) requires *m/z* 541.3794.
HPLC purity 90.8%, t_R = 1.46 min.

69. Synthesis of 3-(3-(4-(isopropylamino)phenyl)propyl)phenol (92)

Compound (**92**) was synthesized by dissolving (*E*)-3-(3-hydroxyphenyl)-1-(4-(isopropylamino)phenyl)prop-2-en-1-one (0.200 g; 0.74 mmol) in a solution of EtOAc:H_2O (3:1 v/v) with $Pd(OH)_2$/C (0.060 g). The reaction mixture was allowed to stir at room temperature under H_2 gas at atmospheric pressure. The reaction was monitored by TLC and filtered through silica gel. The filtrate was dissolved in EtOAc followed by extraction with EtOAc (2 x 50 mL). The organic layer was washed with water (1 x 50 mL) and brine (1 x 20

mL), dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.53 yielded 3-(3-(4-(isopropylamino)phenyl)propyl)phenol (**92**) as a light yellow oil (0.182 g, 91%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.09 – 7.02 (1H, m, H-5"), 6.92 (2H, d, J = 8.5 Hz, H-2', H-6'), 6.68 (1H, d, J = 7.8 Hz, H-4"), 6.58 – 6.54 (2H, m, H-2"), H-6"), 6.48 (2H, d, J = 8.5 Hz, H-3', H-5'), 3.58 – 3.49 (1H, m, -NH-C**H**-), 2.51 (2H, t, J = 7.7 Hz, H-1), 2.46 (2H, t, J = 7.7 Hz, H-3), 1.86 – 1.75 (2H, m, H-2), 1.14 (6H, d, J = 6.3 Hz, 2 x C**H$_3$**) (Plate 69a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.5 (C-3"), 145.4 (C-4'), 144.6 (C-1"), 131.0 (C-1'), 129.4 (C-5"), 129.2 (C-2', C-6'), 120.9 (C-4"), 115.4 (C-6"), 113.7 (C-3', C-5'), 112.6 (C-2"), 44.7 (-NH-**C**H-), 35.3 (H-1), 34.5 (H-3), 33.0 (H-2), 23.1 (2 x **C**H_3) (Plate 69b).
IR (neat): ν_{max} = 2968.47, 1583.66, 1155.39, 799.22, 694.68 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 270.1851, ($C_{18}H_{23}NO + H^+$) requires *m/z* 270.1858.
HPLC purity 96.2%, t_R = 1.96 min.

70. Synthesis of 4-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)butan-2-one (88)

Compound (**88**) was synthesized according to the general procedure for the Mannich reaction given earlier using 4-(3-hydroxyphenyl)butan-2-one (0.050 g; 0.30 mmol), paraformaldehyde (0.023 g; 0.77 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 4-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)butan-2-one (**88**) as a light yellow oil (0.066 g, 84%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 6.88 (1H, d, J = 7.6 Hz, H-5'), 6.65 (1H, d, J = 1.5 Hz, H-2'), 6.61 (1H, dd, J = 7.6, 1.5 Hz, H-6'), 3.65 (2H, s, C**H$_2$**), 3.22 – 2.58 (4H, H-2", H-6"), 2.87 – 2.81 (2H, m, H-2), 2.79 – 2.73 (2H, m, H-3), 2.17 (3H, s, C**H$_3$**), 1.69 – 1.45 (6H, m, H-3", H-4", H-5") (Plate 70a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 208.3 (C-1), 158.1 (C-3'), 141.6 (C-1'), 128.5 (C-5'), 119.4 (C-4'), 118.9 (C-6'), 115.7 (C-2'), 61.9 (**C**H_2), 53.9 (C-2", C-6"), 45.1 (C-3), 30.1 (**C**H_3), 29.5 (C-2), 25.9 (C-3', C-5'), 24.0 (C-4') (Plate 70b).
IR (neat): ν_{max} = 3330.24, 1412.23, 1018.56, 670.11 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 262.1809, ($C_{16}H_{23}NO_2 + H^+$) requires *m/z* 262.1807.

HPLC purity 94.8%, t_R = 1.50 min.

71. Synthesis of 5-ethyl-2-(piperidin-1-ylmethyl)phenol (87)

Compound (**87**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3-ethylphenol (0.035 g; 0.29 mmol), paraformaldehyde (0.018 g; 0.60 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 5-ethyl-2-(piperidin-1-ylmethyl)phenol (**87**) as a light yellow oil (0.038 g, 60%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 6.88 (1H, d, J = 7.6 Hz, H-5), 6.69 (1H, d, J = 1.5 Hz, H-2), 6.62 (1H, dd, J = 7.6, 1.5 Hz, H-6), 3.65 (2H, s, C**H$_2$**), 3.27 – 2.77 (4H, H-2', H-6'), 2.60 (2H, q, J = 7.6 Hz, -C**H$_2$**-CH_3), 1.68 – 1.35 (6H, m, H-3', H-4', H-5'), 1.23 (3H, t, J = 7.6 Hz, C**H$_3$**) (Plate 71a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3), 145.0 (C-1), 128.3 (C-5), 118.9 (C-4), 118.4 (C-6), 115.4 (C-2), 61.9 (**C**H_2), 53.9 (C-2', C-6'), 28.6 (-**C**H_2-CH_3), 25.9 (C-3', C-5'), 24.1 (C-4'), 15.5 (**C**H_3) (Plate 71b).
IR (neat): ν_{max} = 2932.98, 1276.06, 859.42, 783.64 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 220.1547, ($C_{14}H_{21}NO + H^+$) requires *m/z* 220.1549.
HPLC purity 94.4%, t_R = 1.53 min.

72. Synthesis of 5-phenethyl-2-(piperidin-1-ylmethyl)phenol (89)

Compound (**89**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3-phenethylphenol (0.100 g; 0.51 mmol), paraformaldehyde (0.037 g; 1.23 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.51 yielded 5-phenethyl-2-(piperidin-1-ylmethyl)phenol (**89**) as a light yellow oil (0.138 g, 92%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.19 (2H, d, J = 7.4 Hz, H-3', H-5'), 7.15 – 7.06 (3H, m, H-2', H-4', H-6'), 6.78 (1H, d, J = 7.6 Hz, H-5"), 6.62 (1H, d, J = 1.5 Hz, H-2"), 6.52 (1H, dd, J = 7.6, 1.5 Hz, H-6"), 3.55 (2H, s, C**H$_2$**), 2.84 – 2.79 (2H, m, H-1), 2.78 – 2.72 (2H, m, H-2), 2.84 – 2.27 (4H, H-2'", H-6'"), 1.57 – 1.31 (6H, m, H-3'", H-4'", H-5'") (Plate 72a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3"), 142.6 (C-1'), 142.0 (C-1"), 128.5 (C-5"), 128.4 (C-2', C-3', C-5', C-6'), 125.9 (C-4'), 119.3 (C-4"), 119.0 (C-6"),

116.0 (C-2"), 62.0 (**C**H_2), 53.9 (C-2"', C-6"'), 37.9 (C-1), 37.8 (C-2), 25.9 (C-3"', C-5"'), 24.1 (C-4"') (Plate 72b).

IR (neat): ν_{max} = 2934.23, 1451.71, 750.13, 697.36 cm^{-1}

Found (TOF MS ES) $[M+H]^+$ 296.2021, ($C_{20}H_{25}NO + H^+$) requires *m/z* 296.2014.

HPLC purity 90.4%, t_R = 1.56 min.

73. Synthesis of 4-cinnamoylbenzamide (120)

Compound (**120**) was synthesized by overnight refluxing of 4-cinnamoylbenzonitrile (0.200 g; 0.86 mmol) in acetic acid in the presence of a catalytic amount of H_2SO_4. The crude reaction mixture was separated by column chromatography (T:A 5:5, 1.5 cm x 15 cm) which yielded the product as a colourless oil, 4-cinnamoylbenzamide (**120**) (0.198g, 92%).

^{1}H NMR δ (600 MHz, Acetone-d_6, Me_4Si) 8.22 (2H, d, J = 8.5 Hz, H-3', H-5'), 8.04 (2H, d, J = 8.5 Hz, H-2', H-6'), 7.98 (1H, d, J = 15.5 Hz, H-3), 7.94 – 7.90 (2H, m, H-2", H-6"), 7.78 (1H, d, J = 15.5 Hz, H-2), 7.50 – 7.44 (3H, m, H-3", H-4", H-5") (Plate 73a). ^{13}C NMR δ (150 MHz, Acetone-d_6, Me_4Si) 189.4 (C-1), 167.6 (**C**O-NH_2), 145.0 (C-3), 139.9 (C-1'), 138.5 (C-4'), 135.1 (C-1"), 131.3 (C-4"), 129.5 (C-2', C-6'), 129.4 (C-3', C-5'), 129.0 (C-2", C-6"), 128.4 (C-3", C-5"), 122.5 (C-2) (Plate 73b).

Found (TOF MS ES) 274.0844, ($C_{16}H_{13}NO_2$ + Na) requires *m/z* 274.0884.

74. Synthesis of 4-(3-phenylpropyl)benzamide (91)

Compound (**91**) was synthesized according to the general procedure using 4-cinnamoylbenzamide (**120**) (0.100 g; 0.39 mmol), H_2 gas and $Pd(OH)_2$/C (0.060 g). The crude reaction mixture was separated by column chromatography (T:A 5:5).

The fraction R_f 0.50 yielded 4-(3-phenylpropyl)benzamide (**91**) as a light yellow oil (0.065 g, 68%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.76 (2H, d, J = 8.2 Hz, H-3', H-5'), 7.34 – 7.17 (7H, H-2', H-6', H-2", H-3", H-4", H-5", H-6"), 2.72 (2H, t, J = 7.5 Hz, H-1), 2.67 (2H, t, J = 7.5 Hz, H-3), 2.03 – 1.96 (2H, m, H-2) (Plate 74a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 169.3 (**C**O), 146.9 (C-1'), 141.9 (C-1"), 130.9 (C-4'), 128.7 (C-3", C-5"), 128.5 (C-2", C-6"), 128.4 (C-2', C-6'), 127.5 (C-3', C-5'), 125.9 (C-4"), 35.4 (C-1), 35.3 (C-3), 32.7 (C-2) (Plate 74b).

IR (neat): ν_{max} = 3386.49, 3166.58, 2936.22, 1646.87, 1615.38, 694.26, 650.24 cm^{-1}

Found (TOF MS ES) $[M+H]^+$ 262.1209, ($C_{16}H_{17}NONa + H^+$) requires *m/z* 262.1208.
HPLC purity 95.9%, t_R = 3.60 min.

75. Synthesis of 1-benzylpiperidine (85)

Compound (**85**) was synthesized using benzylbromide (0.100 g; 0.58 mmol) and piperdine (0.1 mL; 1.0 mmol) in dry DMF (20 mL). The reaction mixture was refluxed overnight and the crude mixture was separated by column chromatography (T:A 8:2, 1.5 cm x 15 cm).

The fraction R_f 0.55 yielded 1-benzylpiperidine as a light brown oil (**85**) (0.085 g, 84%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.38 – 7.22 (5H, m, H-2', H-3', H-4', H-5', H-6'), 3.49 (2H, s, C**H$_2$**), 2.40 (4H, s, H-2", H-6"), 1.62 – 1.55 (4H, m, H-3", H-5"), 1.45 (2H, s, H-4") (Plate 75a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 138.6 (C-1'), 129.3 (C-2', C-6'), 128.1 (C-3', C-5'), 126.8 (C-4'), 63.9 (**C**H_2), 54.5 (C-2", C-6"), 26.0 (C-3", C-5"), 24.4 (C-4") (Plate 75b).
IR (neat): ν_{max} = 2960.69, 1276.06, 977.69, 814.37, 783.64 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 176.1357, ($C_{12}H_{17}N + H^+$) requires *m/z* 176.1359.

76. Synthesis of 3-(3-(naphthalen-2-yl)propyl)phenol (121)

Compound (**121**) was synthesized by dissolving (*E*)-3-(3-hydroxyphenyl)-1-(naphthalen-2-yl)prop-2-en-1-one (0.300 g; 1.1 mmol) in a solution of EtOAc:H_2O (3:1 v/v) with $Pd(OH)_2$/C (0.060 g). The reaction mixture was allowed to stir at room temperature under H_2 gas at atmospheric pressure. The reaction was monitored by TLC and filtered through silica gel. The filtrate was dissolved in EtOAc followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.50 yielded 3-(3-(naphthalen-2-yl)propyl)phenol (**121**) as a light yellow oil (0.286 g, 99%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.75 – 7.65 (3H, m, H-3', H-7', H-10'), 7.55 – 7.23 (4H, H-2', H-6', H-8', H-9'), 7.09 – 7.04 (1H, m, H-5"), 6.72 – 6.66 (1H, m, H-4"), 6.60 – 6.54 (2H, m, H-2", H-6"), 2.72 (2H, t, J = 7.5 Hz, H-3), 2.55 (2H, t, J = 7.5 Hz, H-1), 1.95 (2H, m, H-2) (Plate 76a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 155.5 (C-3"), 144.3 (C-1"), 139.8 (C-1'), 133.7 (C-5'), 132.0 (C-4'), 129.5 (C-5"), 127.9 (C-10'), 127.6 (C-7'), 127.5

(C-2'), 127.4 (C-6'), 126.5 (C-3'), 125.9 (C-8'), 125.1 (C-9'), 121.1 (C-6''), 115.4 (C-2''), 112.7 (C-4''), 35.5 (C-1), 35.3 (C-3), 32.6 (C-2) (Plate 76b).
IR (neat): ν_{max} = 2922.92, 1588.45, 1454.19, 1154.24, 694.89 cm^{-1}
Found (TOF MS ES) $[M-H]^+$ 261.1280, ($C_{19}H_{18}O$ - H^+) requires *m/z* 261.1279.

77. Synthesis of 5-(3-(naphthalen-2-yl)propyl)-2-(piperidin-1-ylmethyl)phenol (95)

Compound (**95**) was synthesized according to the general procedure for the Mannich reaction given earlier using 3-(3-(naphthalen-2-yl)propyl)phenol (**121**) (0.100 g; 0.38 mmol), paraformaldehyde (0.022 g; 0.73 mmol), and piperidine (0.1 mL; 1.0 mmol) as starting materials. The resulting crude reaction mixture was separated by column chromatography (H:EtOAc 7:3, 1.5 cm x 15 cm).

The fraction R_f 0.51 yielded 5-(3-(naphthalen-2-yl)propyl)-2-(piperidin-1-ylmethyl)phenol (**95**) as a light yellow oil (0.068 g, 50%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.75 – 7.23 (7H, m, H-2', H-3', H-6', H-7', H-8', H-9', H-10'), 6.79 (1H, d, J = 7.6 Hz, H-5''), 6.61 (1H, d, J = 1.5 Hz, H-2''), 6.53 (1H, dd, J = 7.6, 1.5 Hz, H-6''), 3.56 (2H, s, C**H$_2$**), 3.00 – 2.21 (4H, H-2''', H-6'''), 2.73 (2H, t, J = 7.5 Hz, H-1), 2.54 (2H, t, J = 7.5 Hz, H-3), 2.02 – 1.86 (2H, m, H-2), 1.59 – 1.35 (6H, m, H-3''', H-4''', H-5''') (Plate 77a). ^{13}C NMR δ (150 MHz, $CDCl_3$, Me_4Si) 158.0 (C-3''), 143.0 (C-1''), 139.9 (C-1'), 133.6 (C-4'), 132.0 (C-5'), 128.3 (C-5''), 127.8 (C-2'), 127.6 (C-6'), 127.4 (C-7', C-10'), 126.4 (C-3'), 125.8 (C-8'), 125.1 (C-9'), 119.1 (C-6''), 119.0 (C-4''), 116.0 (C-2''), 61.9 (**C**H_2), 53.9 (C-2''', C-6'''), 35.6 (C-1), 35.2 (C-3), 32.7 (C-2), 25.9 (C-3''', C-5'''), 24.1 (C-4''') (Plate 77b).
IR (neat): ν_{max} = 2928.51, 1451.29, 988.17, 809.31 cm^{-1}
Found (TOF MS ES) $[M+H]^+$ 360.2247, ($C_{25}H_{29}NO$ + H^+) requires *m/z* 360.2249.

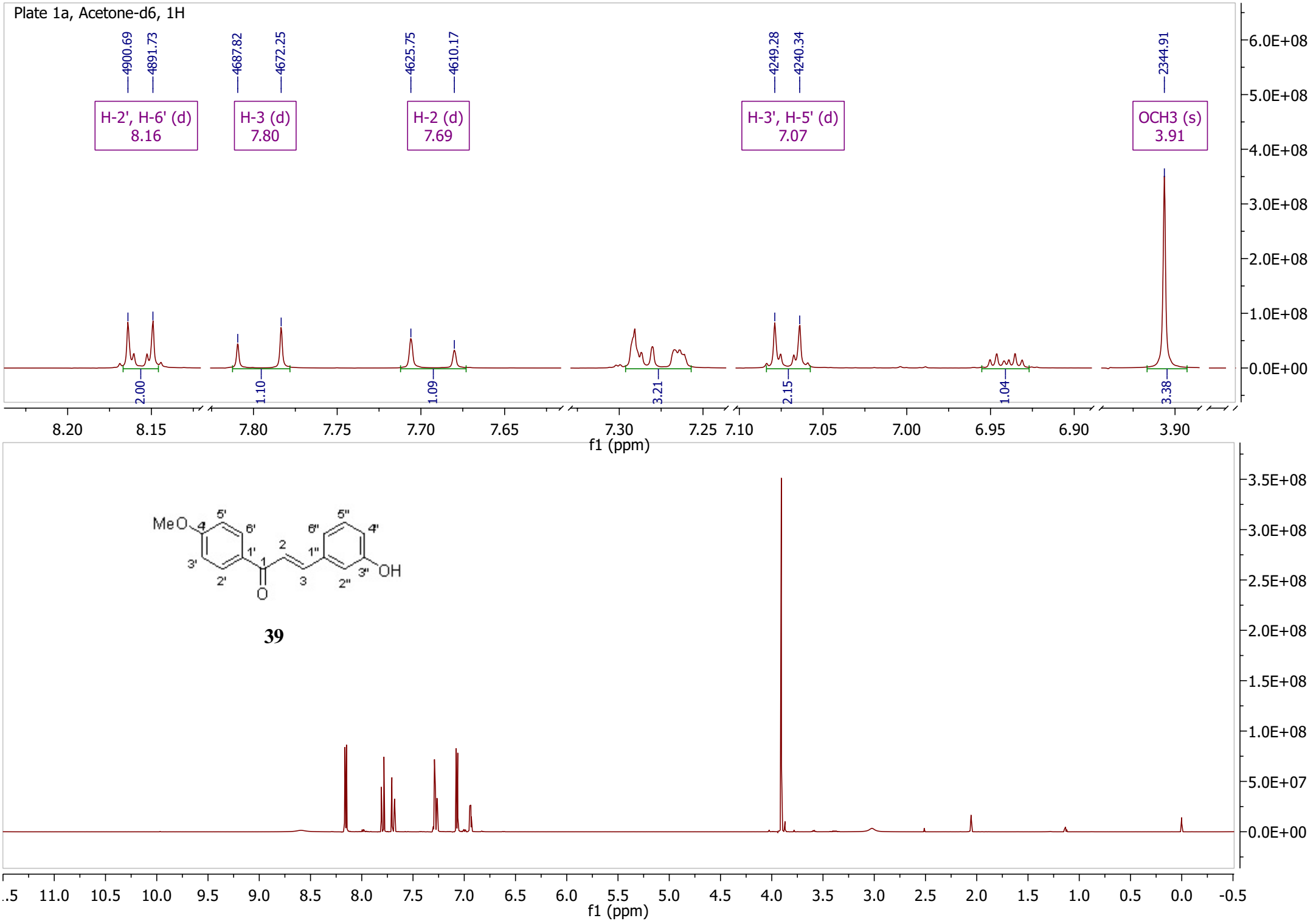


Plate 1a, Acetone-d6, 1H
4900.69
4891.73
4687.82
4672.25
4625.75
4610.17
4249.28
4240.34
2344.91
H-2', H-6' (d)
8.16
H-3 (d)
7.80
H-2 (d)
7.69
H-3', H-5' (d)
7.07
OCH3 (s)
3.91
2.00
1.10
1.09
3.21
2.15
1.04
3.38
f1 (ppm)
MeO
OH
39
f1 (ppm)

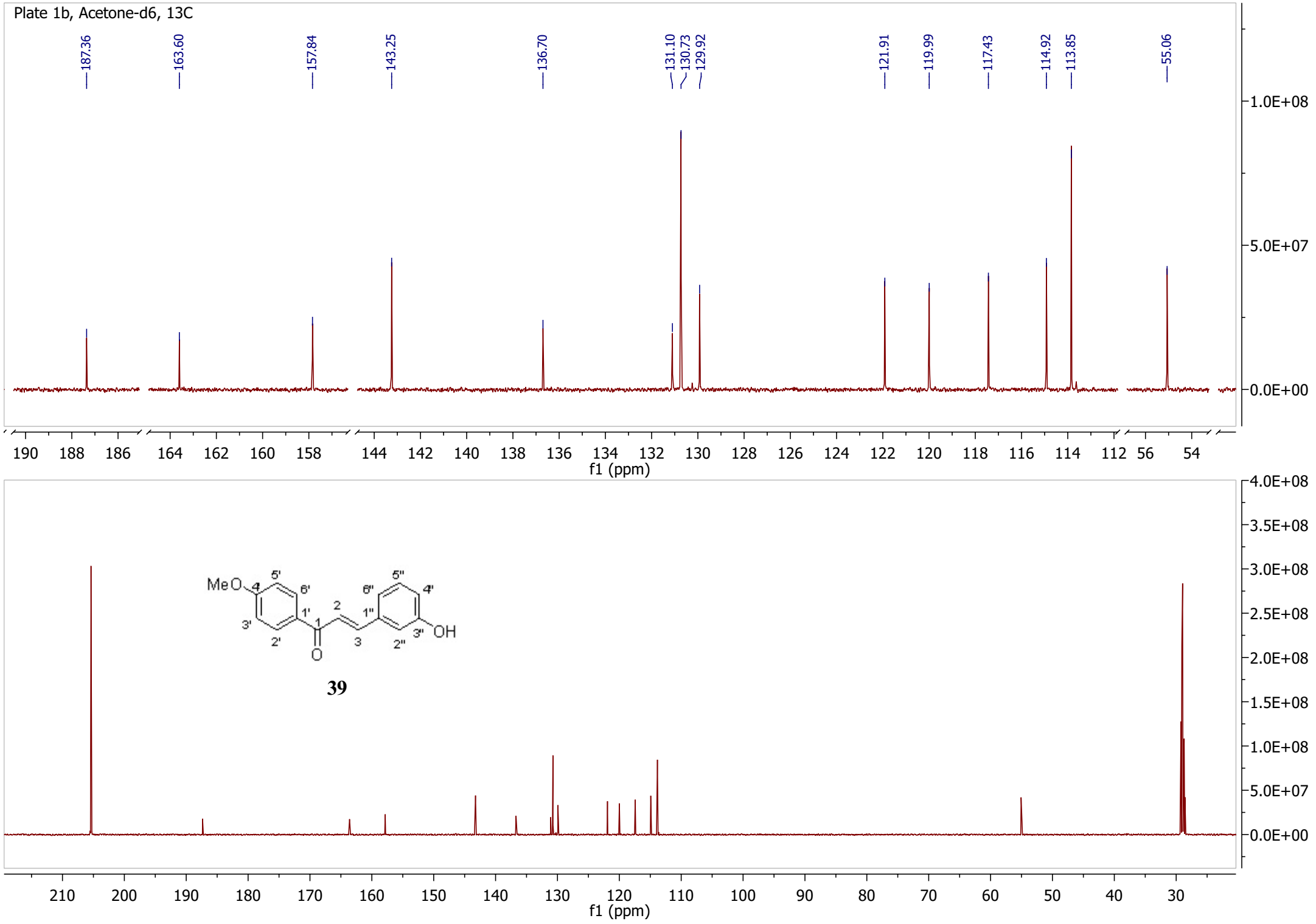


Plate 1b, Acetone-d6, 13C
187.36
163.60
157.84
143.25
136.70
131.10
130.73
129.92
121.91
119.99
117.43
114.92
113.85
55.06
1.0E+08
5.0E+07
0.0E+00
190 188 186 164 162 160 158 144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112 56 54
f1 (ppm)
MeO
OH
O
39
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

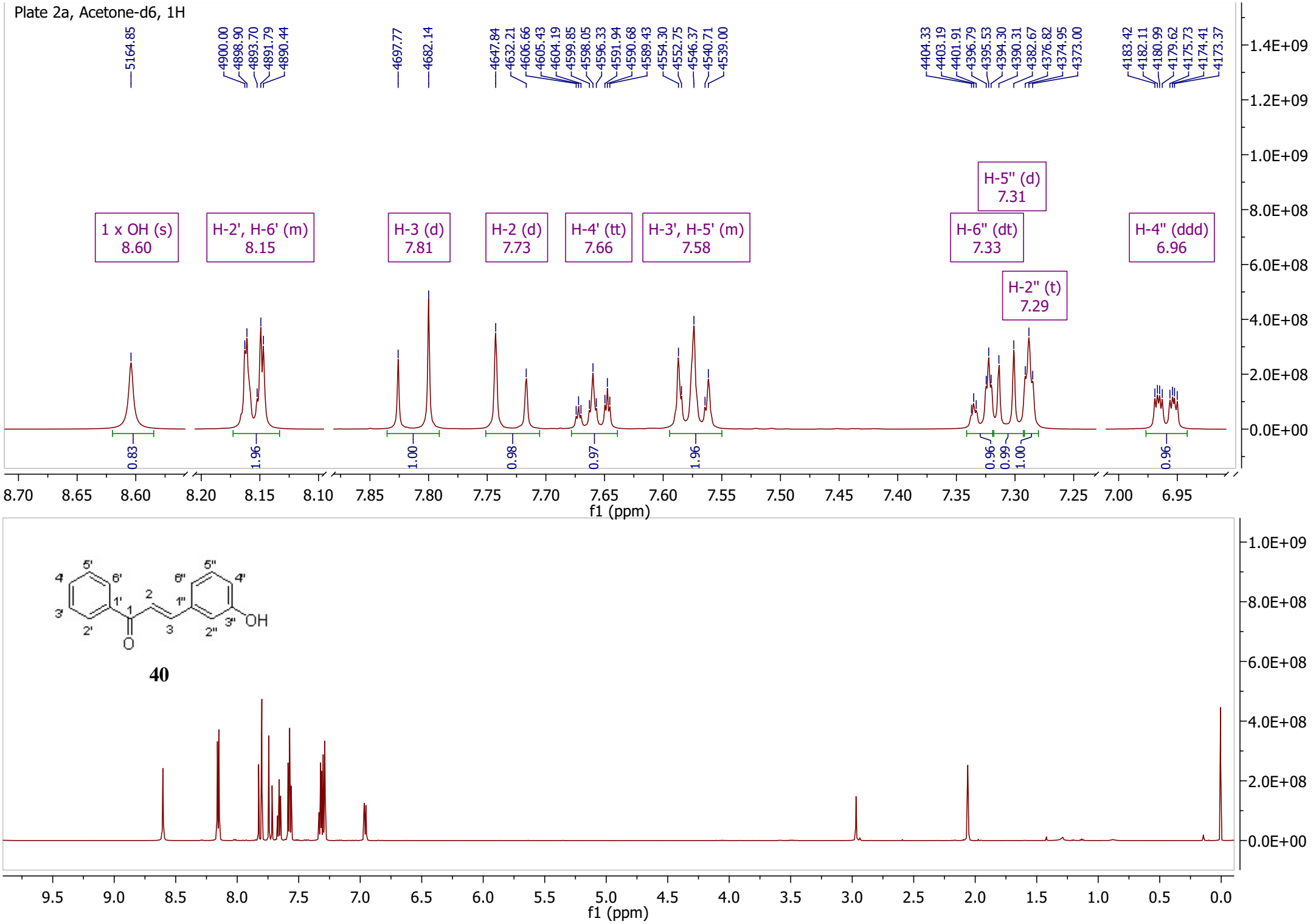
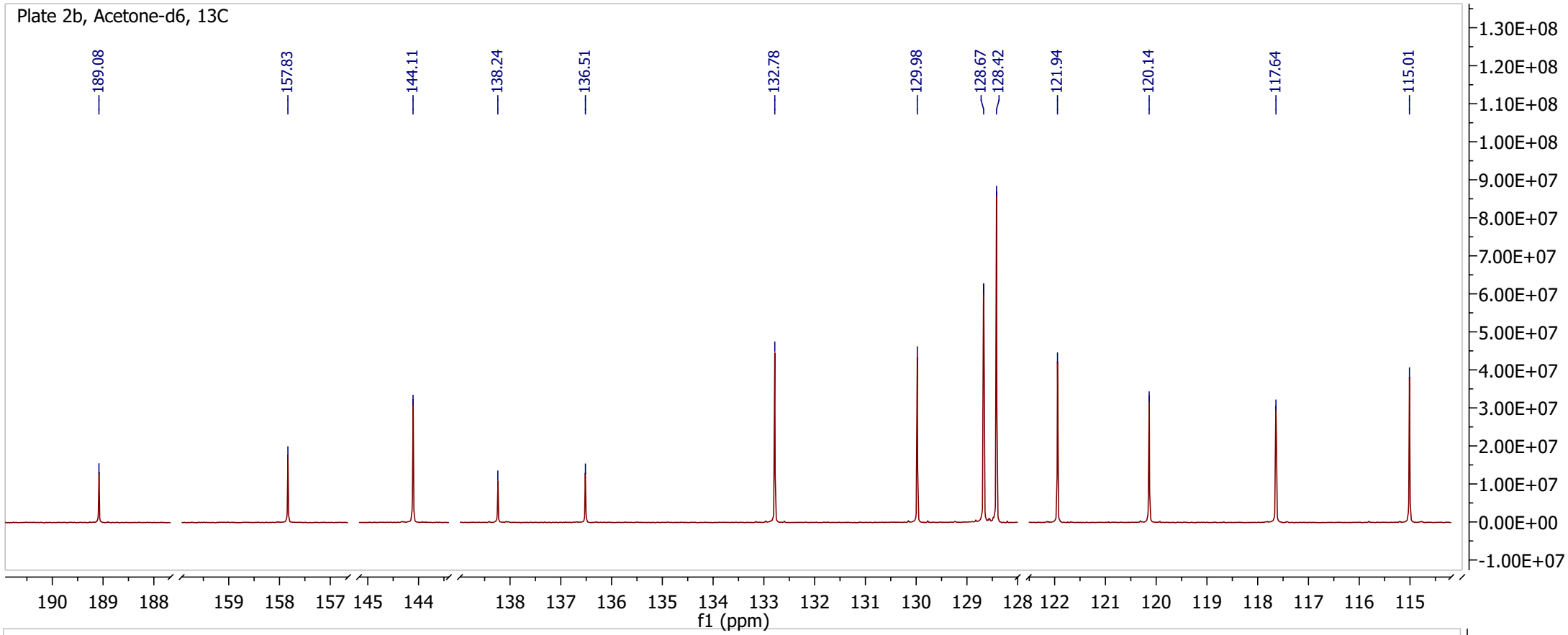
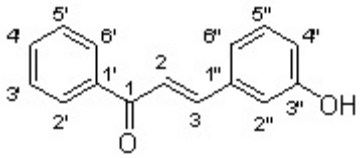


Plate 2a, Acetone-d6, 1H
5164.85
4900.00
4898.90
4893.70
4891.79
4890.44
4697.77
4682.14
4647.84
4632.21
4606.66
4605.43
4604.19
4599.85
4598.05
4596.33
4591.94
4590.68
4589.43
4554.30
4552.75
4546.37
4540.71
4539.00
4404.33
4403.19
4401.91
4396.79
4395.53
4394.30
4390.31
4382.67
4376.82
4374.95
4373.00
4183.42
4182.11
4180.99
4179.62
4175.73
4174.41
4173.37
1 x OH (s)
8.60
H-2', H-6' (m)
8.15
H-3 (d)
7.81
H-2 (d)
7.73
H-4' (tt)
7.66
H-3', H-5' (m)
7.58
H-5" (d)
7.31
H-6" (dt)
7.33
H-2" (t)
7.29
H-4" (ddd)
6.96
0.83
1.96
1.00
0.98
0.97
1.96
0.96
0.99
1.00
0.96
f1 (ppm)
OH
O
40
f1 (ppm)

Plate 2b, Acetone-d6, 13C





40

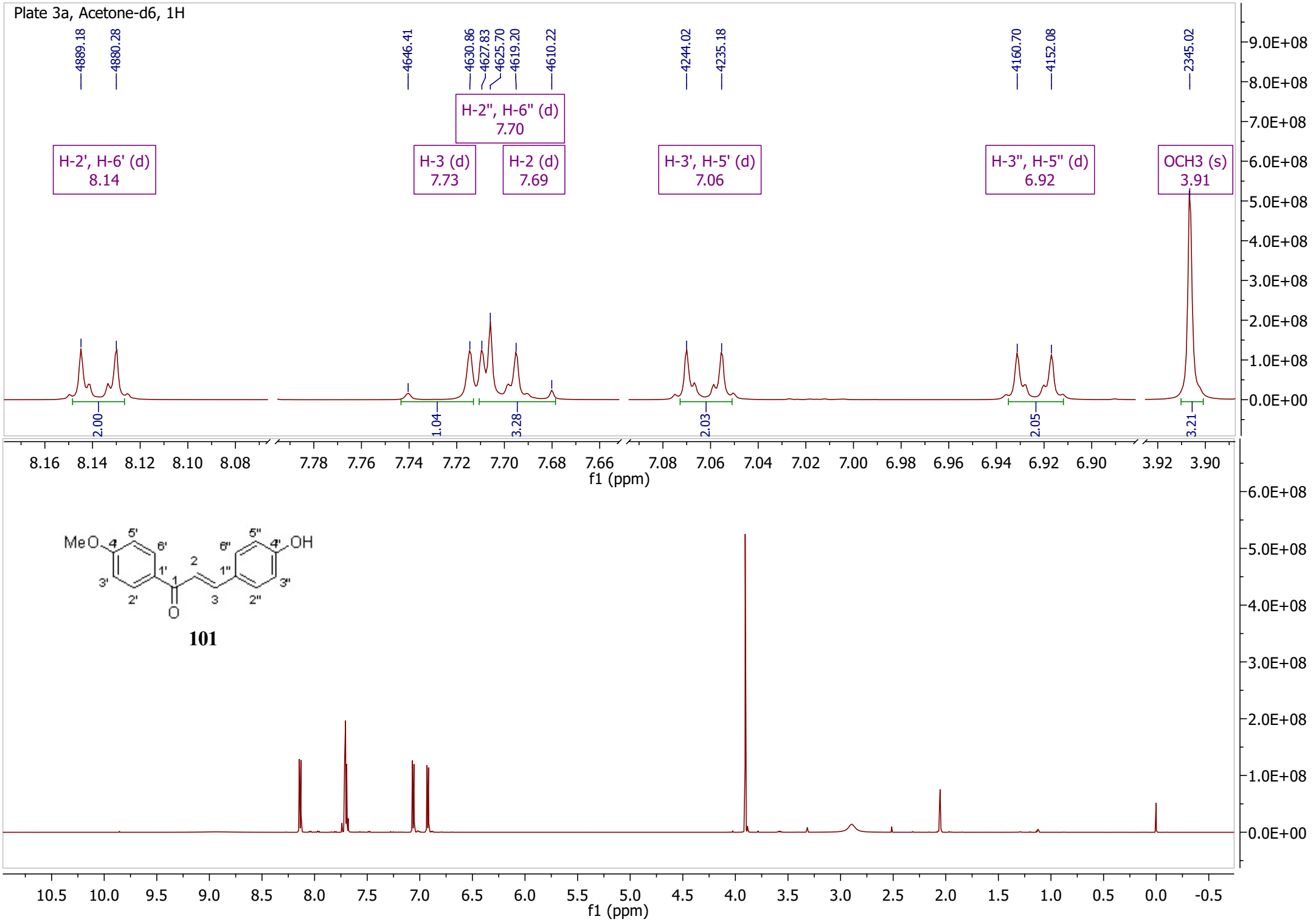
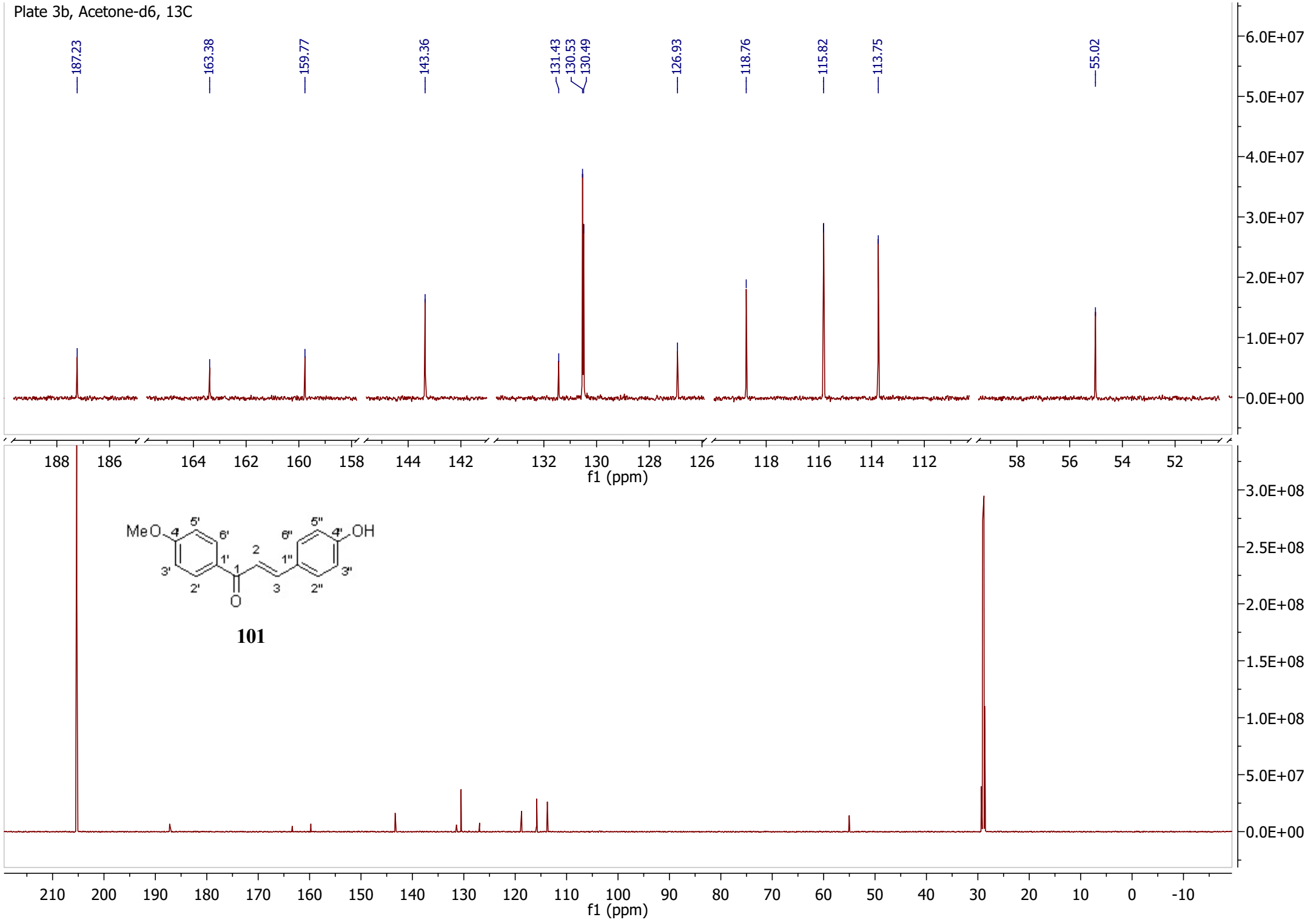


Plate 3a, Acetone-d6, 1H
4889.18
4880.28
4646.41
4630.86
4627.83
4625.70
4619.20
4610.22
4244.02
4235.18
4160.70
4152.08
2345.02
H-2', H-6' (d) 8.14
H-3 (d) 7.73
H-2", H-6" (d) 7.70
H-2 (d) 7.69
H-3', H-5' (d) 7.06
H-3", H-5" (d) 6.92
OCH3 (s) 3.91
2.00
1.04
3.28
2.03
2.05
3.21
f1 (ppm)
MeO
OH
101
f1 (ppm)

Plate 3b, Acetone-d6, 13C



101

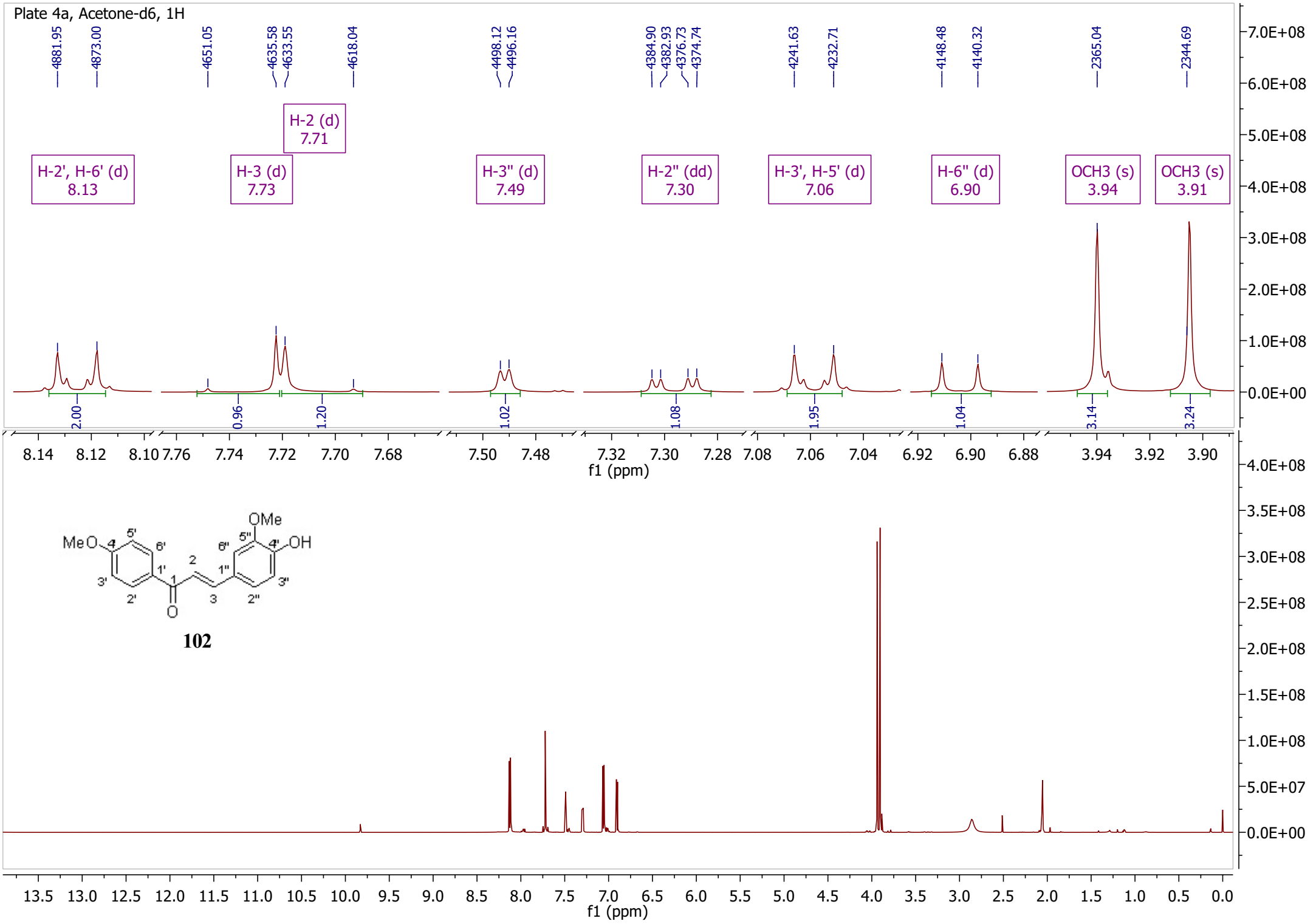


Plate 4a, Acetone-d6, 1H
4881.95
4873.00
4651.05
4635.58
4633.55
4618.04
4498.12
4496.16
4384.90
4382.93
4376.73
4374.74
4241.63
4232.71
4148.48
4140.32
2365.04
2344.69
H-2 (d)
7.71
H-2', H-6' (d)
8.13
H-3 (d)
7.73
H-3" (d)
7.49
H-2" (dd)
7.30
H-3', H-5' (d)
7.06
H-6" (d)
6.90
OCH3 (s)
3.94
OCH3 (s)
3.91
2.00
0.96
1.20
1.02
1.08
1.95
1.04
3.14
3.24
f1 (ppm)
f1 (ppm)
MeO
OMe
OH
102

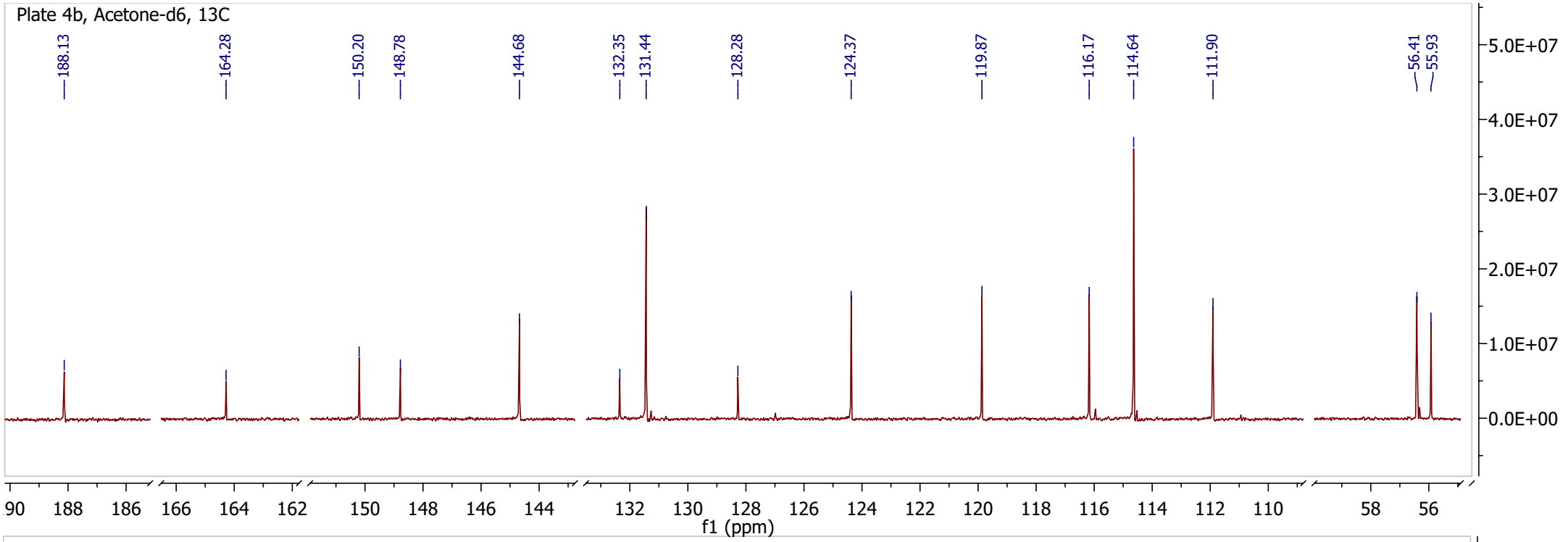
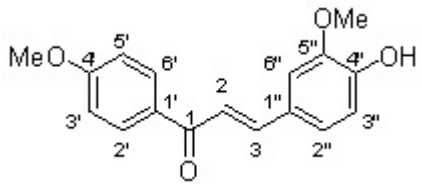


Plate 4b, Acetone-d6, 13C
188.13
164.28
150.20
148.78
144.68
132.35
131.44
128.28
124.37
119.87
116.17
114.64
111.90
56.41
55.93
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
90 188 186 166 164 162 150 148 146 144 132 130 128 126 124 122 120 118 116 114 112 110 58 56
f1 (ppm)


MeO
OMe
OH
5'
6'
4'
1'
2'
3'
1
2
3
1"
2"
3"
4"
5"
6"
O

102

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

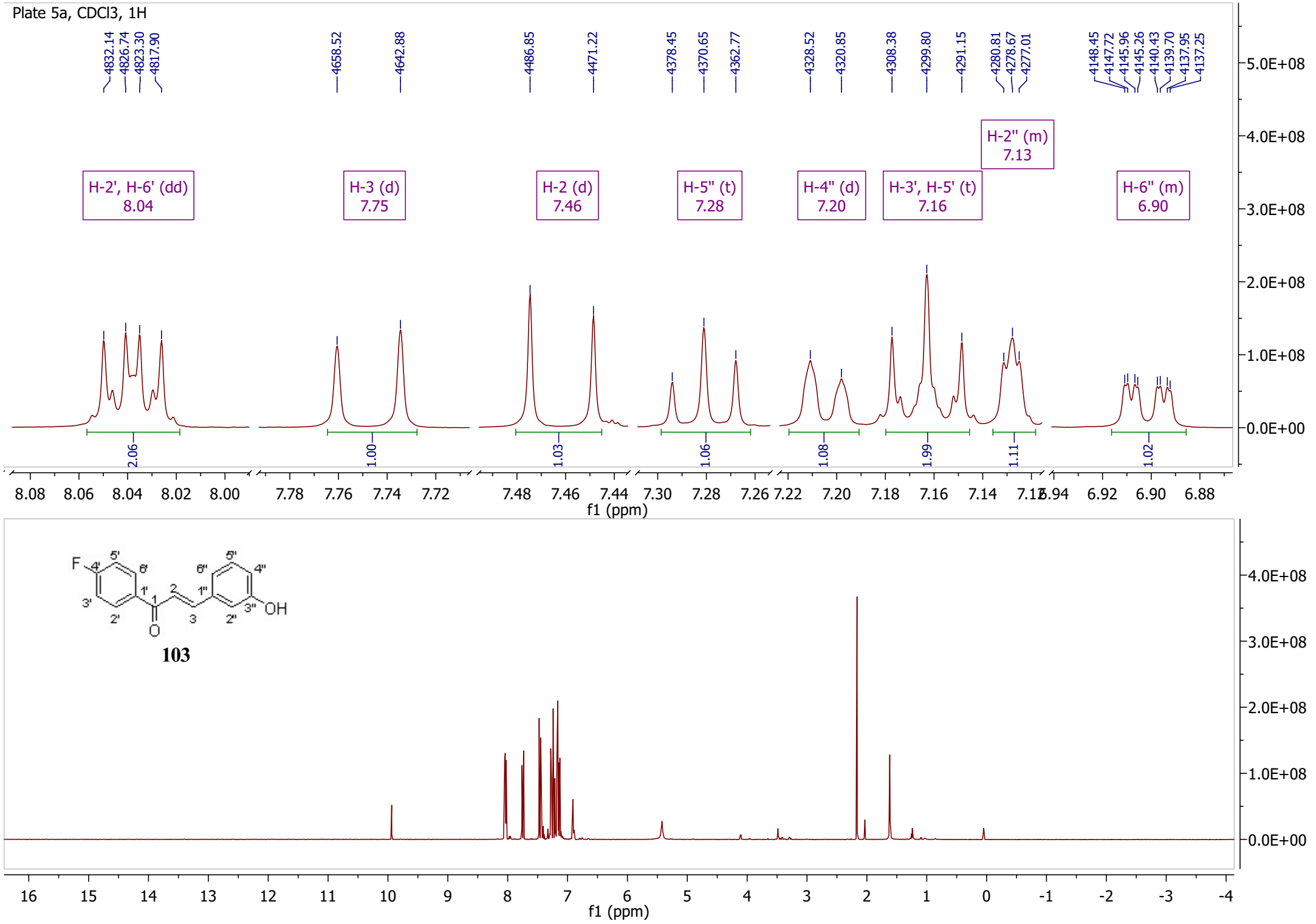


Plate 5a, CDCl3, 1H
4832.14
4826.74
4823.30
4817.90
4658.52
4642.88
4486.85
4471.22
4378.45
4370.65
4362.77
4328.52
4320.85
4308.38
4299.80
4291.15
4280.81
4278.67
4277.01
4148.45
4147.72
4145.96
4145.26
4140.43
4139.70
4137.95
4137.25
H-2', H-6' (dd)
8.04
H-3 (d)
7.75
H-2 (d)
7.46
H-5" (t)
7.28
H-4" (d)
7.20
H-3', H-5' (t)
7.16
H-2" (m)
7.13
H-6" (m)
6.90
2.06
1.00
1.03
1.06
1.08
1.99
1.11
1.02
f1 (ppm)
F
OH
O
103
f1 (ppm)

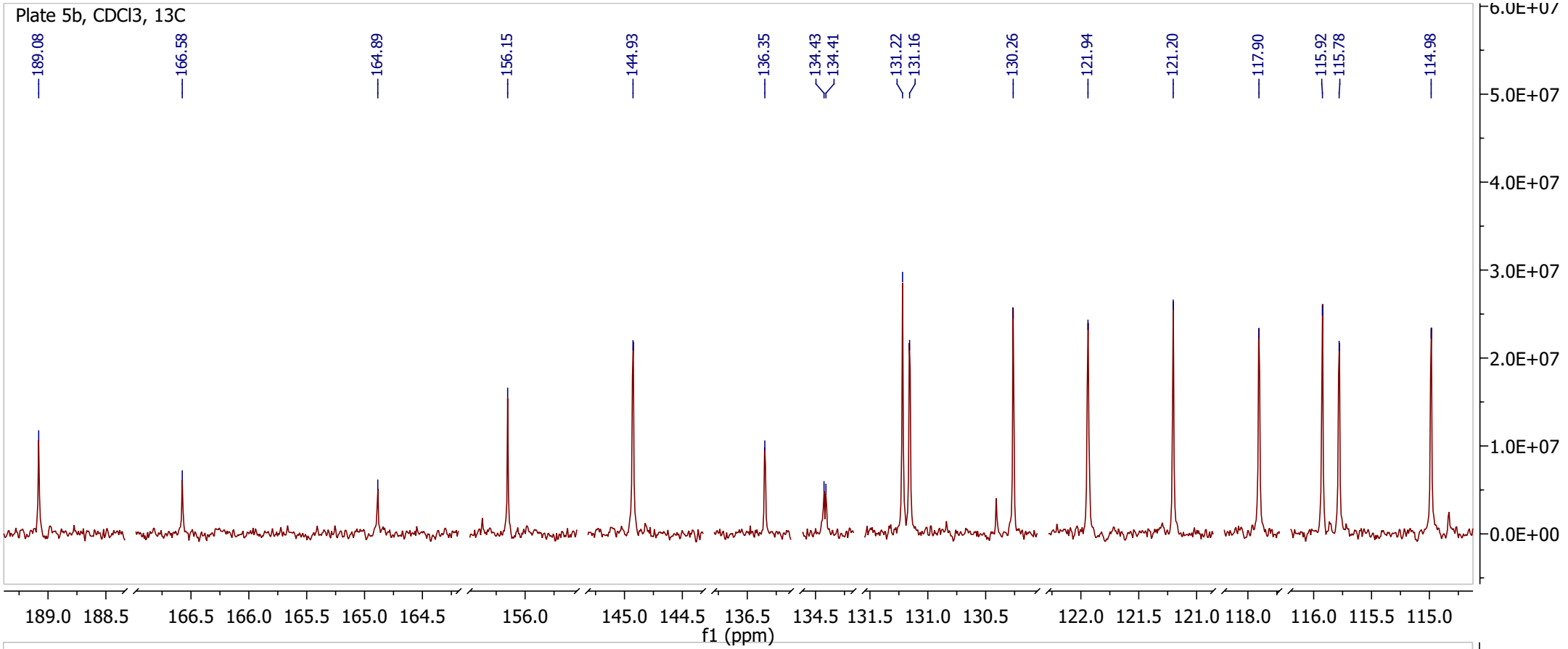
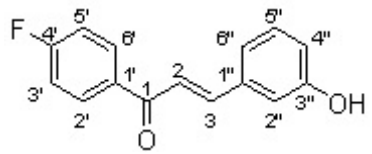


Plate 5b, CDCl3, 13C
189.08
166.58
164.89
156.15
144.93
136.35
134.43
134.41
131.22
131.16
130.26
121.94
121.20
117.90
115.92
115.78
114.98
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
189.0 188.5 166.5 166.0 165.5 165.0 164.5 156.0 145.0 144.5 136.5 134.5 131.5 131.0 130.5 122.0 121.5 121.0 118.0 116.0 115.5 115.0
f1 (ppm)


F
5'
4'
6'
1'
2
1
3'
2'
O
3
1"
6"
5'
4"
2"
3"
OH

103

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

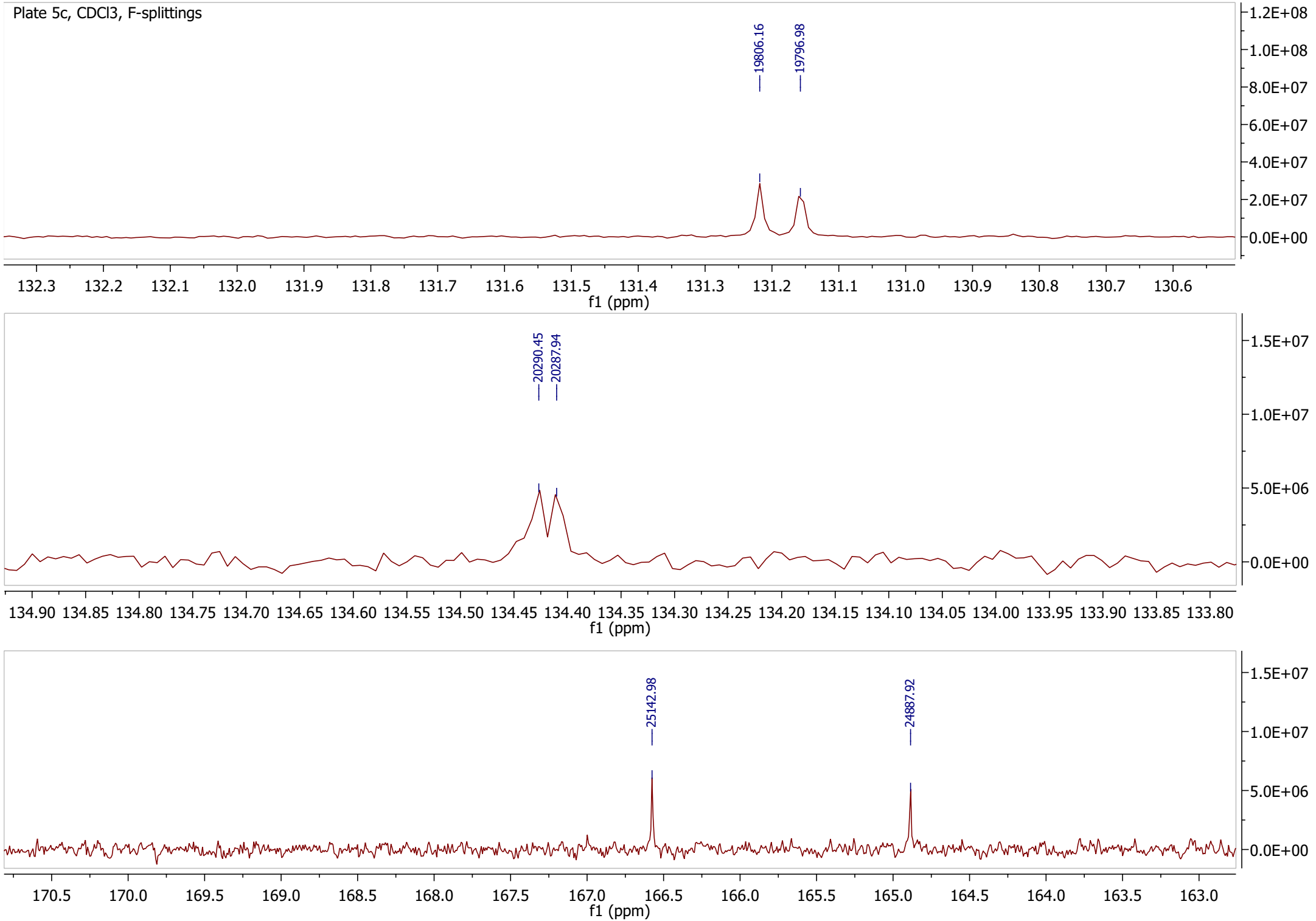


Plate 5c, CDCl3, F-splittings
19806.16
19796.98
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
132.3 132.2 132.1 132.0 131.9 131.8 131.7 131.6 131.5 131.4 131.3 131.2 131.1 131.0 130.9 130.8 130.7 130.6
f1 (ppm)
20290.45
20287.94
1.5E+07
1.0E+07
5.0E+06
0.0E+00
134.90 134.85 134.80 134.75 134.70 134.65 134.60 134.55 134.50 134.45 134.40 134.35 134.30 134.25 134.20 134.15 134.10 134.05 134.00 133.95 133.90 133.85 133.80
f1 (ppm)
25142.98
24887.92
1.5E+07
1.0E+07
5.0E+06
0.0E+00
170.5 170.0 169.5 169.0 168.5 168.0 167.5 167.0 166.5 166.0 165.5 165.0 164.5 164.0 163.5 163.0
f1 (ppm)

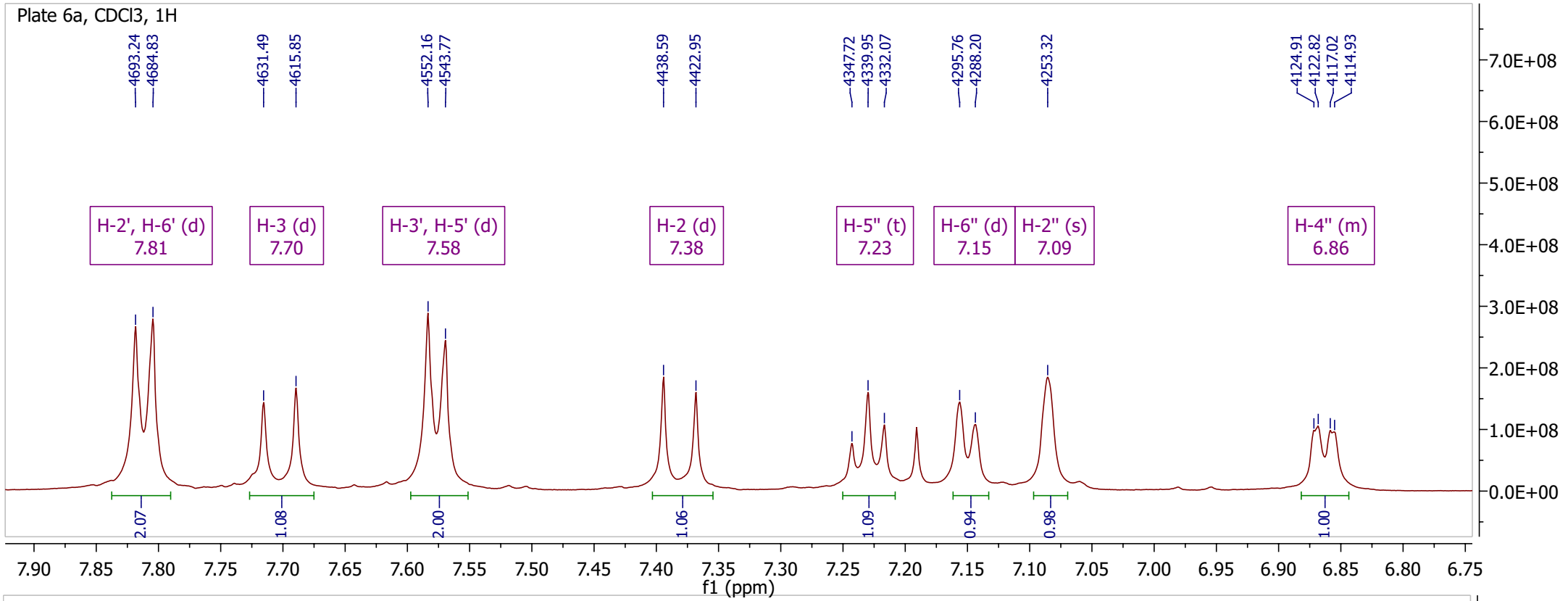
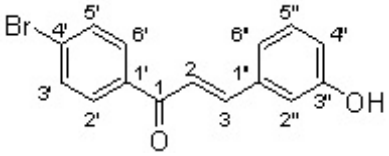


Plate 6a, CDCl3, 1H
4693.24
4684.83
4631.49
4615.85
4552.16
4543.77
4438.59
4422.95
4347.72
4339.95
4332.07
4295.76
4288.20
4253.32
4124.91
4122.82
4117.02
4114.93
H-2', H-6' (d) 7.81
H-3 (d) 7.70
H-3', H-5' (d) 7.58
H-2 (d) 7.38
H-5" (t) 7.23
H-6" (d) 7.15
H-2" (s) 7.09
H-4" (m) 6.86
2.07
1.08
2.00
1.06
1.09
0.94
0.98
1.00
f1 (ppm)


Br
OH
O

104

f1 (ppm)

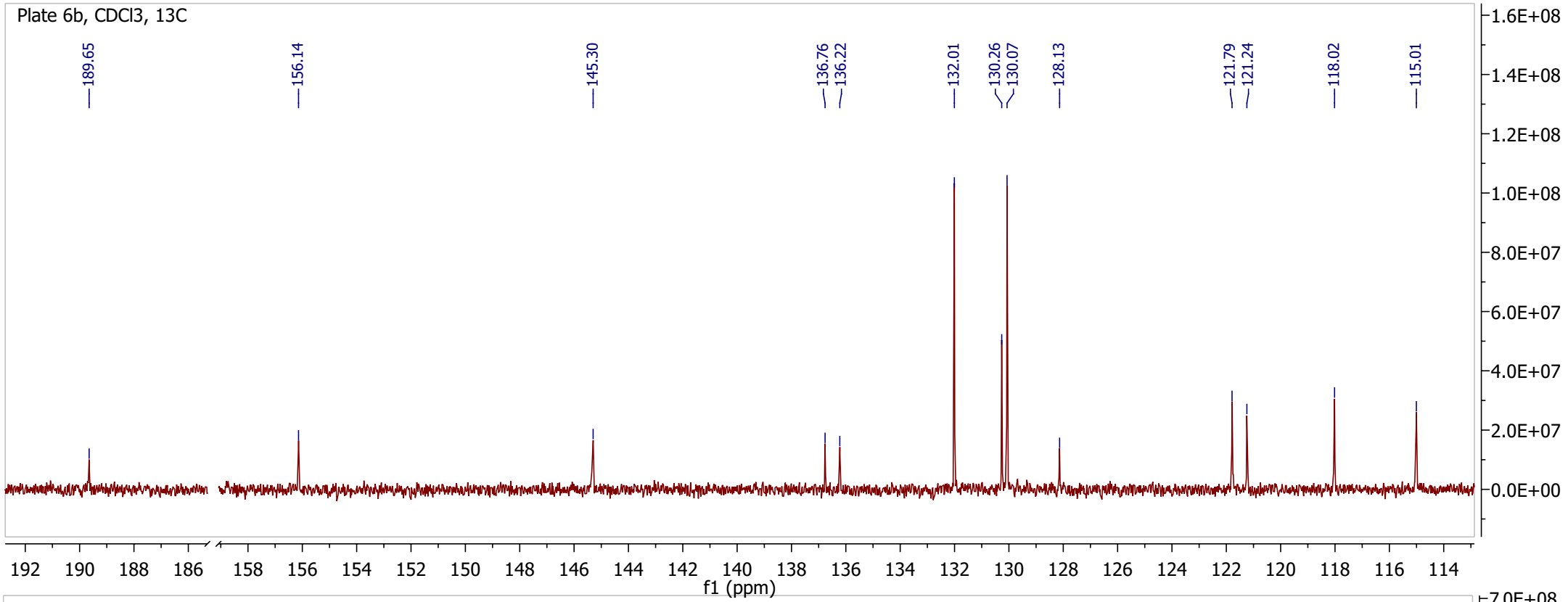
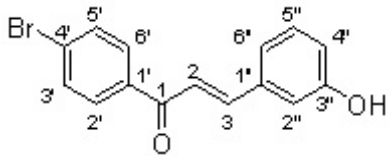


Plate 6b, CDCl3, 13C
189.65
156.14
145.30
136.76
136.22
132.01
130.26
130.07
128.13
121.79
121.24
118.02
115.01
1.6E+08
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
192 190 188 186 158 156 154 152 150 148 146 144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114
f1 (ppm)


Br
5'
4'
6'
1'
2
1"
6"
5"
4"
3'
1
2'
3
2"
3"
OH
O

104

7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

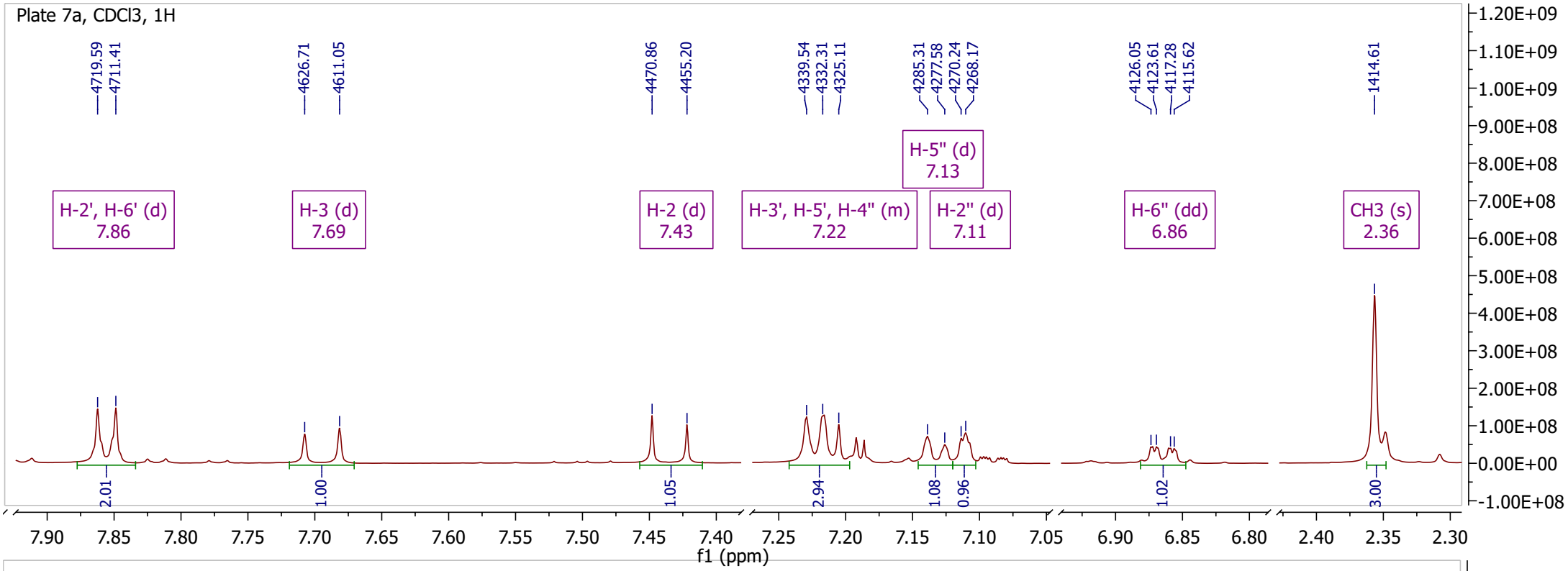
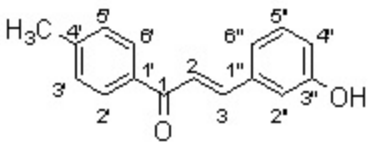


Plate 7a, CDCl3, 1H
4719.59
4711.41
4626.71
4611.05
4470.86
4455.20
4339.54
4332.31
4325.11
4285.31
4277.58
4270.24
4268.17
4126.05
4123.61
4117.28
4115.62
1414.61
H-2', H-6' (d) 7.86
H-3 (d) 7.69
H-2 (d) 7.43
H-3', H-5', H-4" (m) 7.22
H-5" (d) 7.13
H-2" (d) 7.11
H-6" (dd) 6.86
CH3 (s) 2.36
2.01
1.00
1.05
2.94
1.08
0.96
1.02
3.00
f1 (ppm)


H3C
OH
O

105

f1 (ppm)

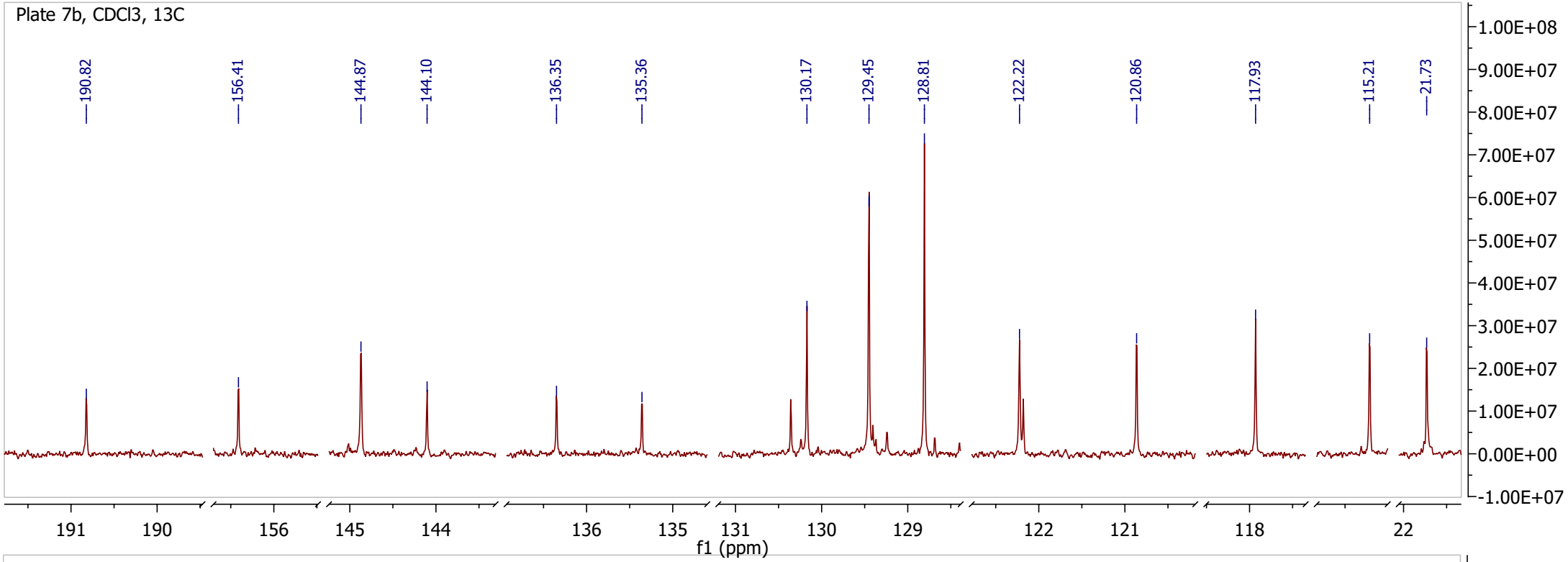
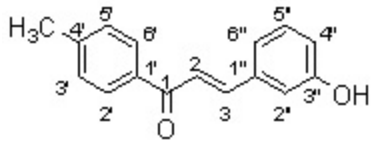


Plate 7b, CDCl3, 13C
190.82
156.41
144.87
144.10
136.35
135.36
130.17
129.45
128.81
122.22
120.86
117.93
115.21
21.73
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
191
190
156
145
144
136
135
131
130
129
122
121
118
22
f1 (ppm)


H3C
4'
5'
6'
1'
2
1"
6"
5"
4'
3'
1
3'
OH
2'
3
2'
O

105

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

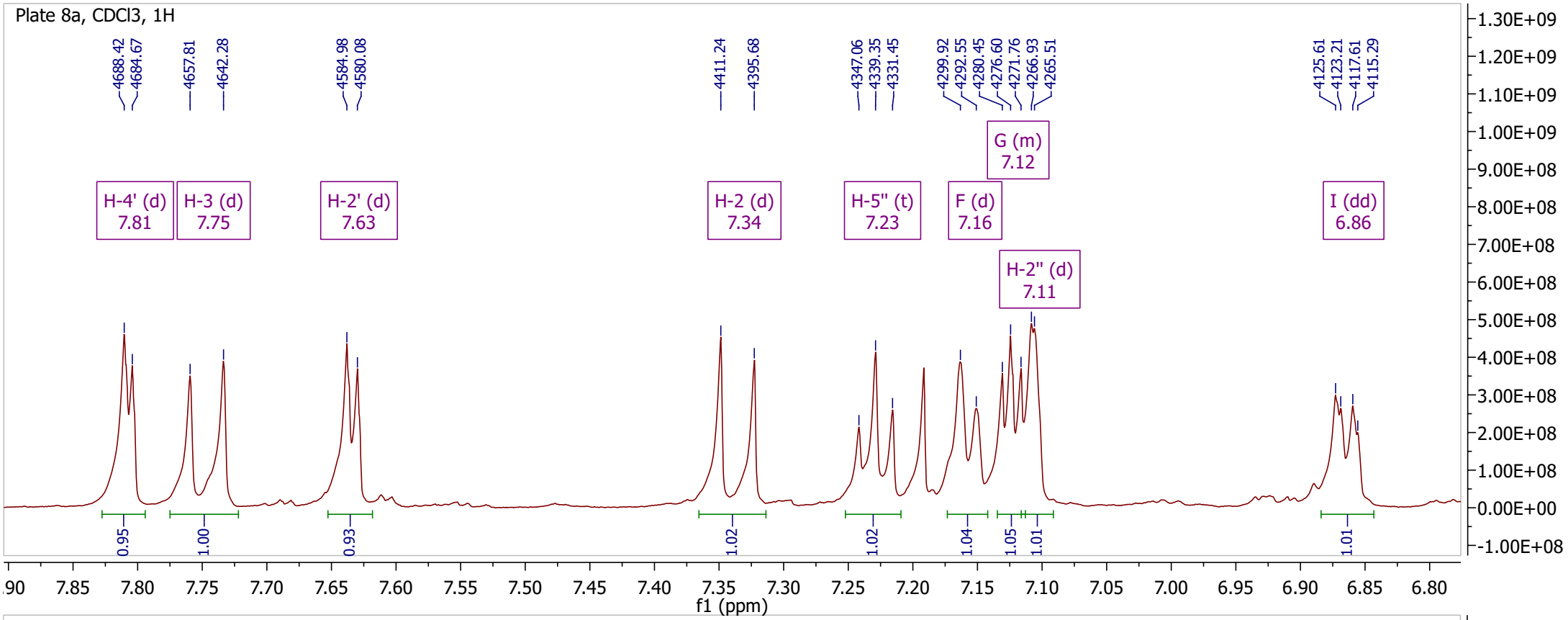
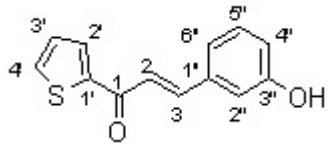


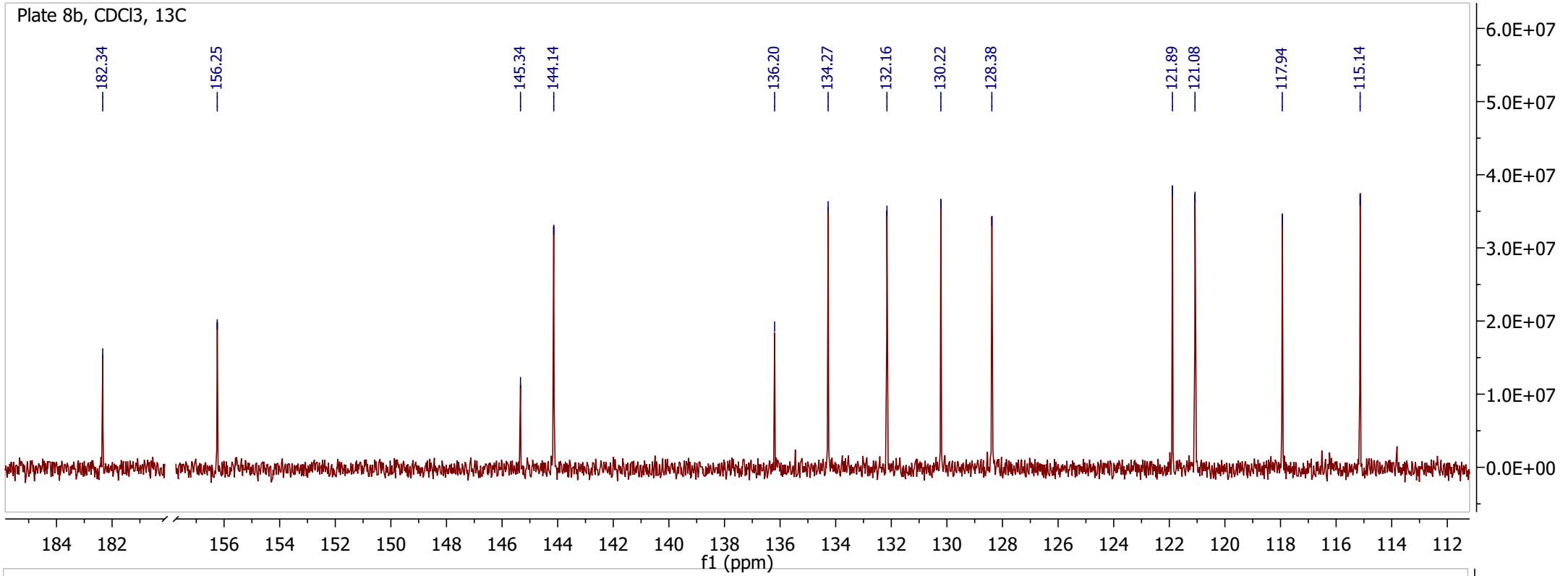
Plate 8a, CDCl3, 1H
4688.42
4684.67
4657.81
4642.28
4584.98
4580.08
4411.24
4395.68
4347.06
4339.35
4331.45
4299.92
4292.55
4280.45
4276.60
4271.76
4266.93
4265.51
4125.61
4123.21
4117.61
4115.29
H-4' (d) 7.81
H-3 (d) 7.75
H-2' (d) 7.63
H-2 (d) 7.34
H-5" (t) 7.23
G (m) 7.12
F (d) 7.16
H-2" (d) 7.11
I (dd) 6.86
0.95
1.00
0.93
1.02
1.02
1.04
1.05
1.01
1.01
f1 (ppm)

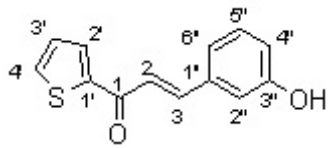

3'
2'
4'
5'
6"
4
S
1'
1
2
1"
3
2"
3"
OH
O

106

f1 (ppm)

Plate 8b, CDCl3, 13C





106

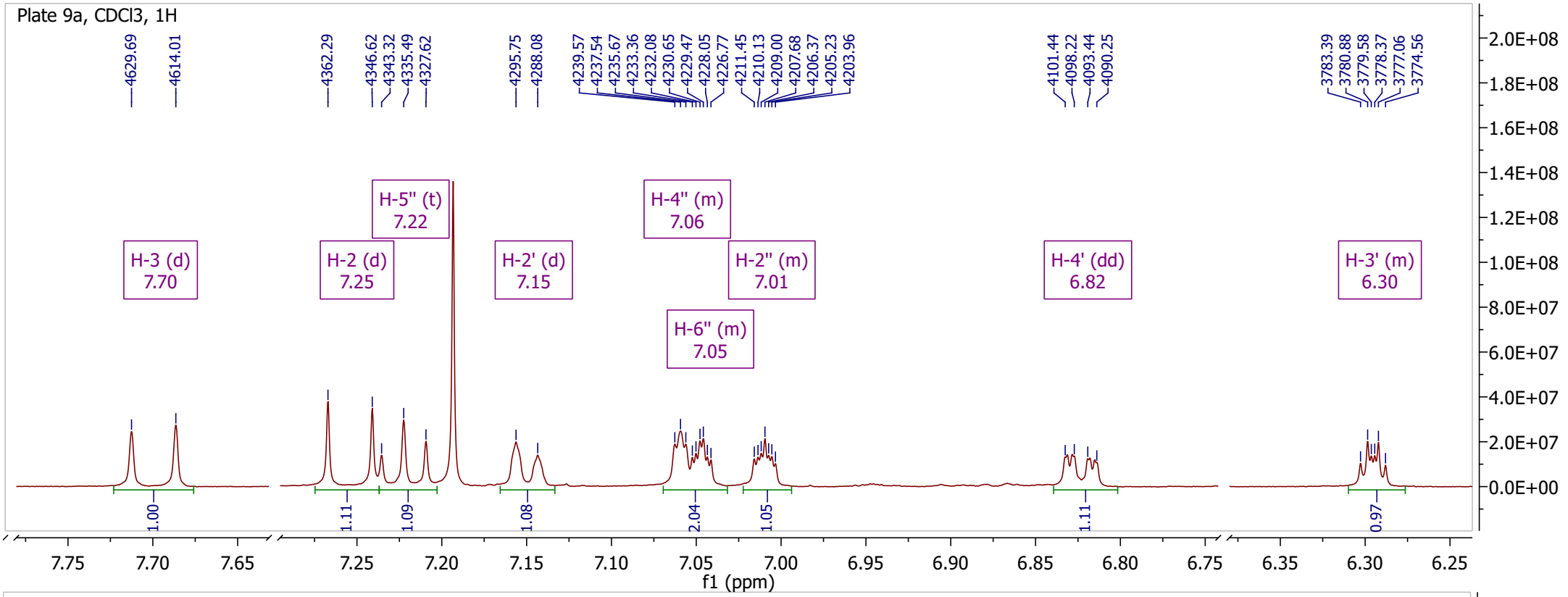
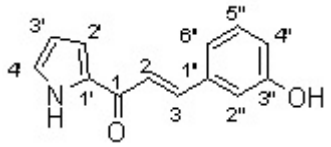


Plate 9a, CDCl3, 1H
4629.69
4614.01
4362.29
4346.62
4343.32
4335.49
4327.62
4295.75
4288.08
4239.57
4237.54
4235.67
4233.36
4232.08
4230.65
4229.47
4228.05
4226.77
4211.45
4210.13
4209.00
4207.68
4206.37
4205.23
4203.96
4101.44
4098.22
4093.44
4090.25
3783.39
3780.88
3779.58
3778.37
3777.06
3774.56
H-3 (d) 7.70
H-2 (d) 7.25
H-5" (t) 7.22
H-2' (d) 7.15
H-4" (m) 7.06
H-6" (m) 7.05
H-2" (m) 7.01
H-4' (dd) 6.82
H-3' (m) 6.30
1.00
1.11
1.09
1.08
2.04
1.05
1.11
0.97
f1 (ppm)


3'
2'
4
5"
6'
4'
1"
2
1
1'
N
H
O
3
2"
3'
OH

107

f1 (ppm)

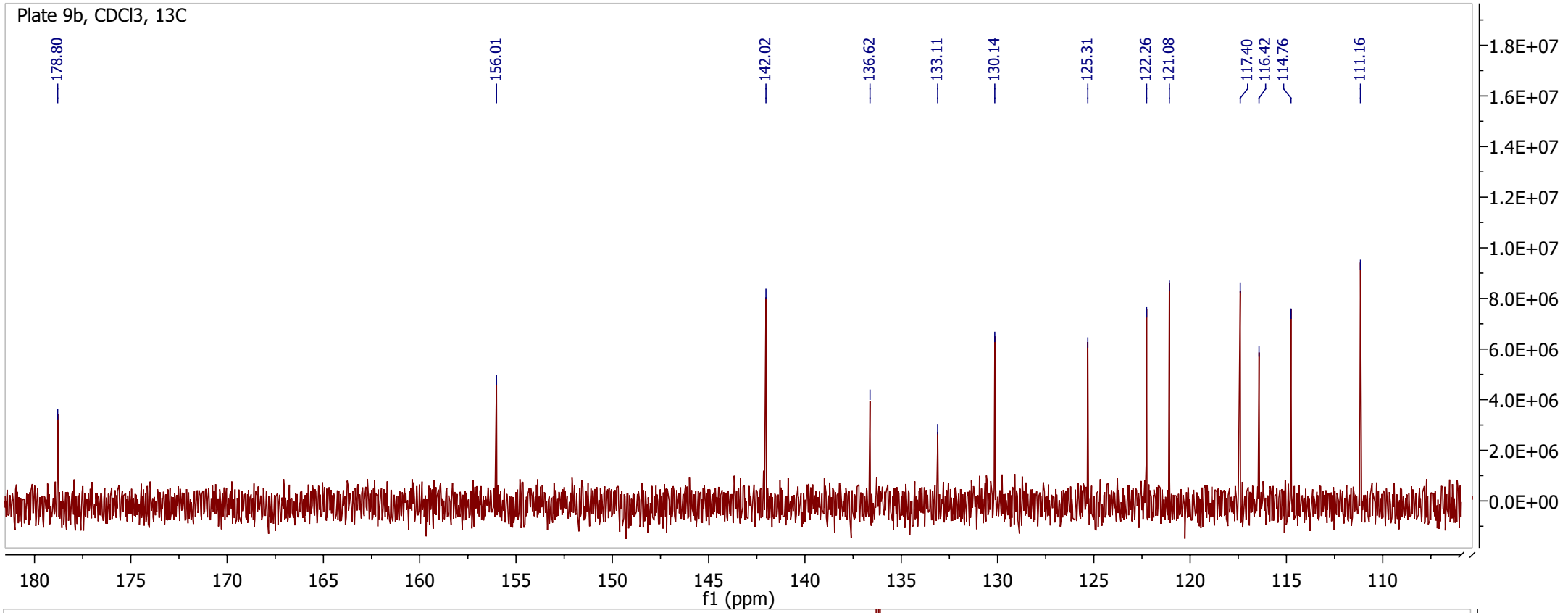
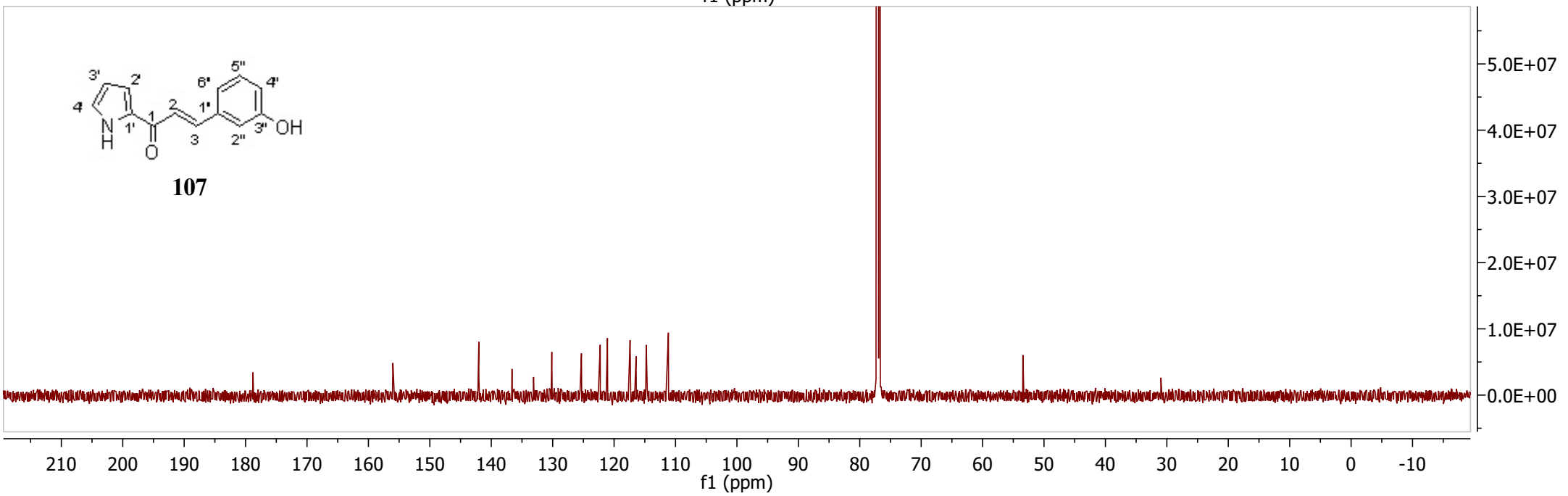


Plate 9b, CDCl3, 13C
178.80
156.01
142.02
136.62
133.11
130.14
125.31
122.26
121.08
117.40
116.42
114.76
111.16
1.8E+07
1.6E+07
1.4E+07
1.2E+07
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
f1 (ppm)


5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

3'
2'
4'
5''
6''
4''
1''
2
1
4
N
H
1'
O
3
2''
3''
OH

107

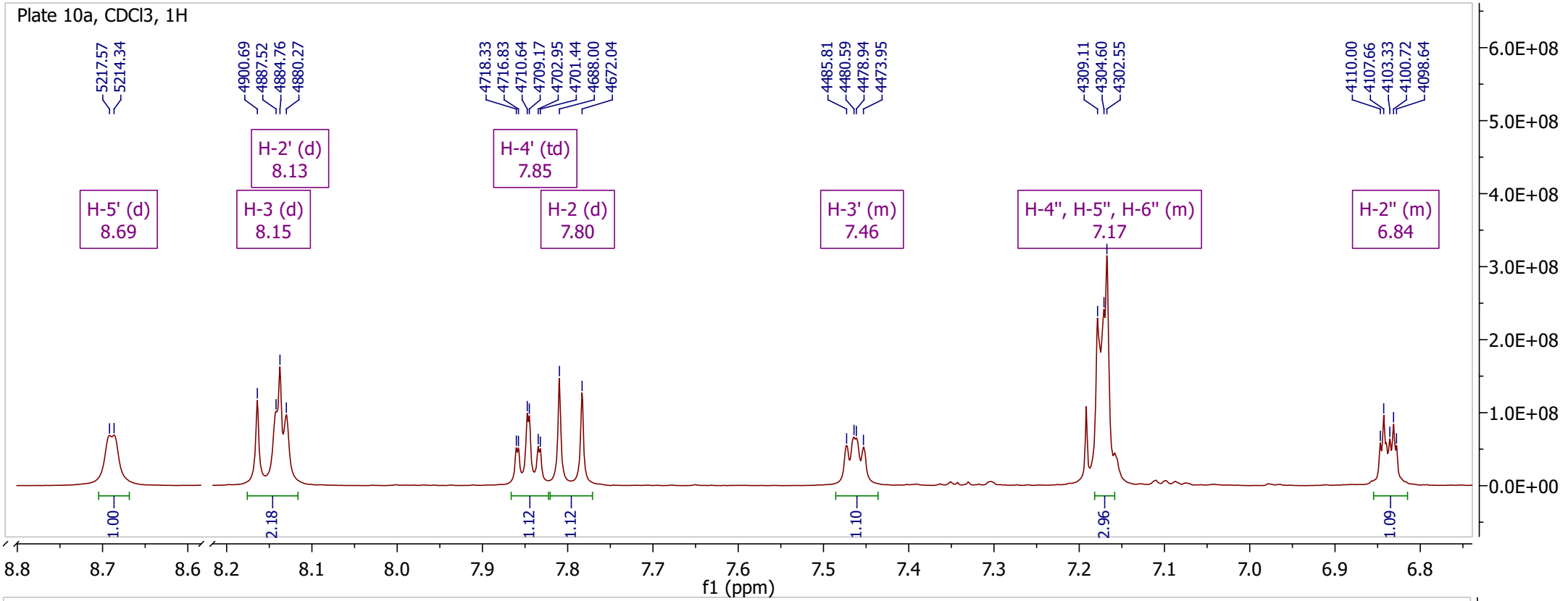
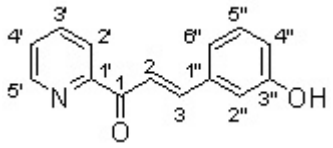


Plate 10a, CDCl3, 1H
5217.57
5214.34
4900.69
4887.52
4884.76
4880.27
4718.33
4716.83
4710.64
4709.17
4702.95
4701.44
4688.00
4672.04
4485.81
4480.59
4478.94
4473.95
4309.11
4304.60
4302.55
4110.00
4107.66
4103.33
4100.72
4098.64
H-5' (d)
8.69
H-2' (d)
8.13
H-3 (d)
8.15
H-4' (td)
7.85
H-2 (d)
7.80
H-3' (m)
7.46
H-4", H-5", H-6" (m)
7.17
H-2" (m)
6.84
1.00
2.18
1.12
1.12
1.10
2.96
1.09
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
8.8
8.7
8.6
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)


3'
4'
2'
5'
N
1'
1
O
2
3
6'
1"
5"
4"
3"
OH
2"

108

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

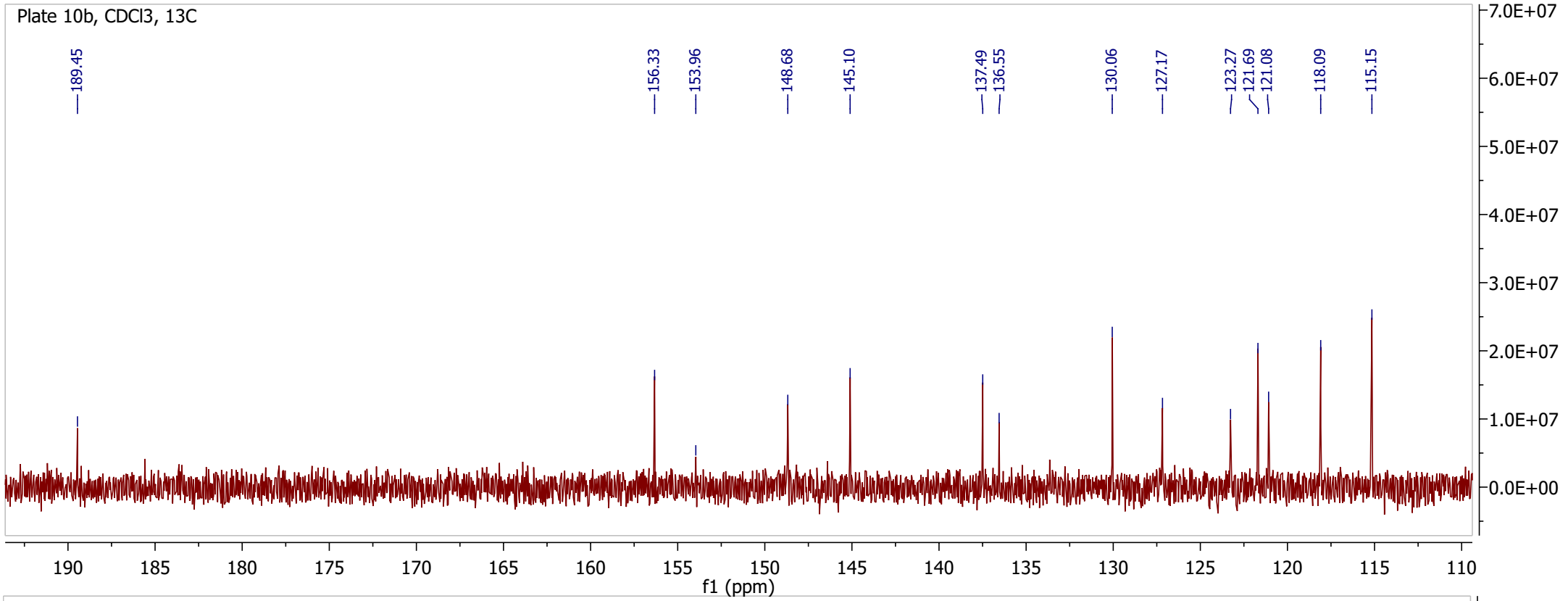
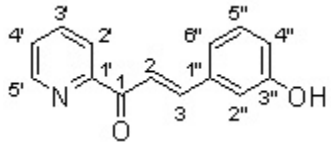


Plate 10b, CDCl3, 13C
189.45
156.33
153.96
148.68
145.10
137.49
136.55
130.06
127.17
123.27
121.69
121.08
118.09
115.15
7.0E+07
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110
f1 (ppm)


3'
4'
2'
5'
N
1'
1
2
3
O
6"
5"
4"
1"
2"
3"
OH

108

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

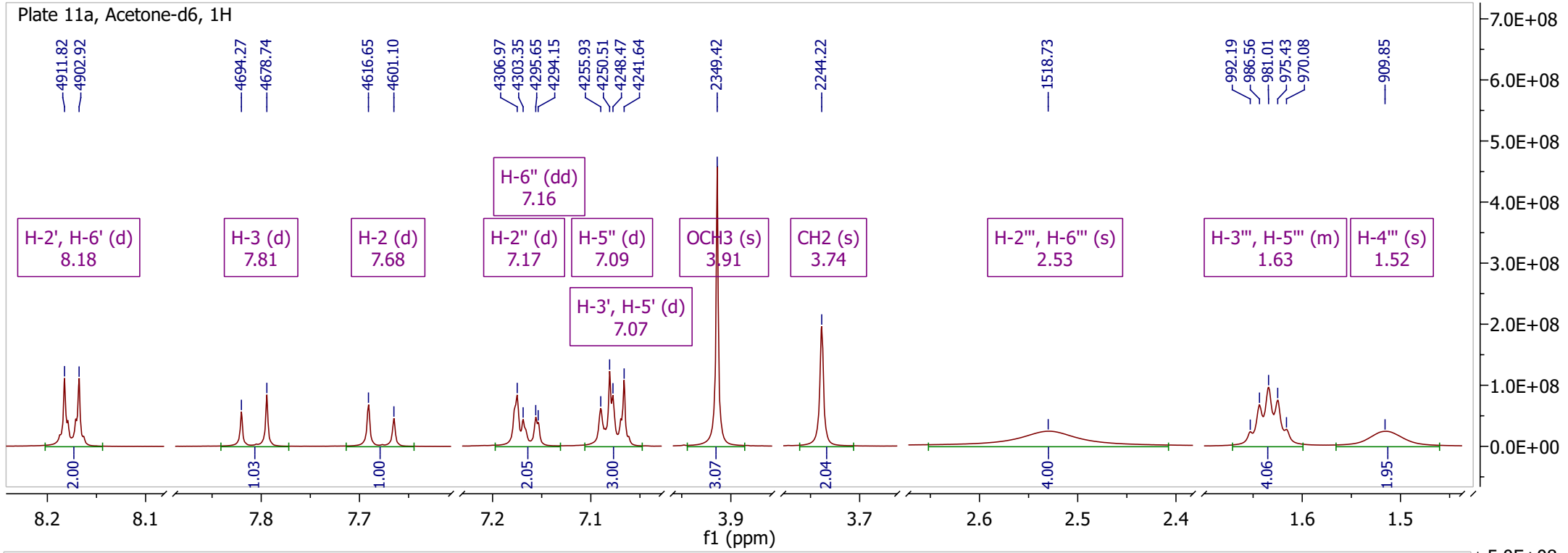
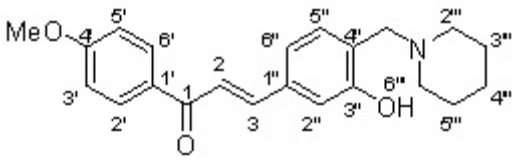


Plate 11a, Acetone-d6, 1H
4911.82
4902.92
4694.27
4678.74
4616.65
4601.10
4306.97
4303.35
4295.65
4294.15
4255.93
4250.51
4248.47
4241.64
2349.42
2244.22
1518.73
992.19
986.56
981.01
975.43
970.08
909.85
H-2', H-6' (d) 8.18
H-3 (d) 7.81
H-2 (d) 7.68
H-6" (dd) 7.16
H-2" (d) 7.17
H-5" (d) 7.09
H-3', H-5' (d) 7.07
OCH3 (s) 3.91
CH2 (s) 3.74
H-2"', H-6"' (s) 2.53
H-3"', H-5"' (m) 1.63
H-4"' (s) 1.52
2.00
1.03
1.00
2.05
3.00
3.07
2.04
4.00
4.06
1.95
8.2
8.1
7.8
7.7
7.2
7.1
3.9
3.7
2.6
2.5
2.4
1.6
1.5
f1 (ppm)
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00


MeO
OH
O
N

41

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00

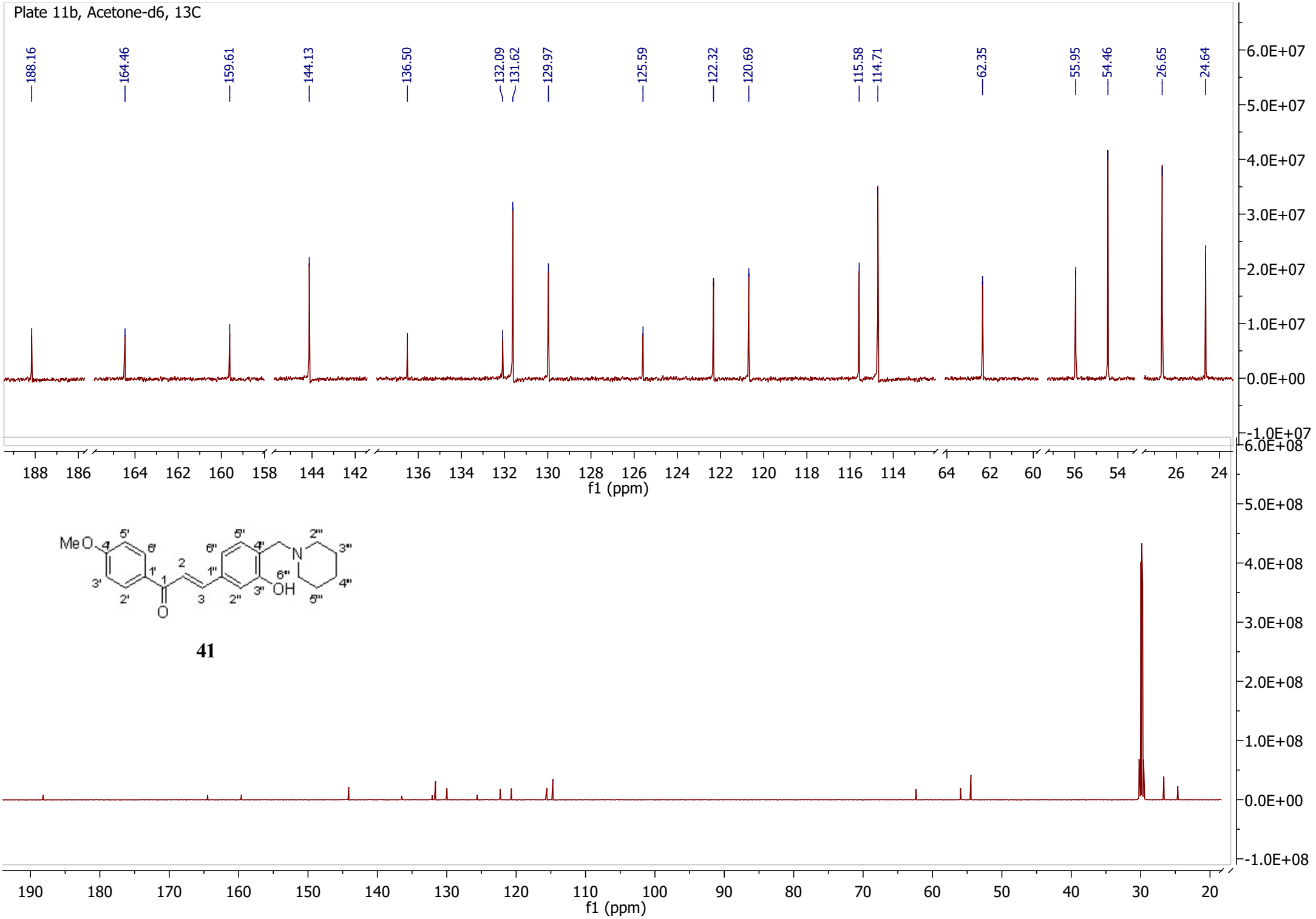


Plate 11b, Acetone-d6, 13C
188.16
164.46
159.61
144.13
136.50
132.09
131.62
129.97
125.59
122.32
120.69
115.58
114.71
62.35
55.95
54.46
26.65
24.64
f1 (ppm)
f1 (ppm)

MeO
OH
O
N

41

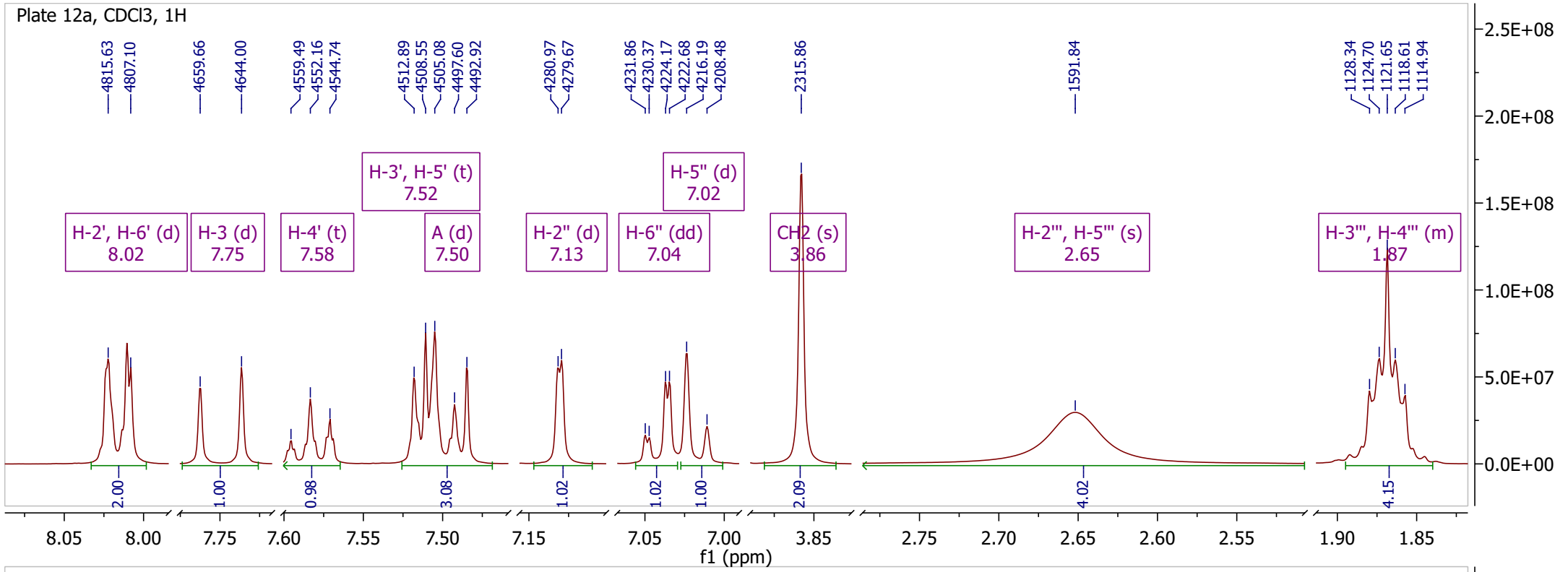
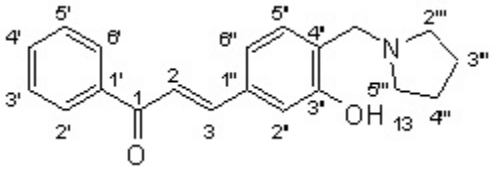


Plate 12a, CDCl3, 1H
4815.63
4807.10
4659.66
4644.00
4559.49
4552.16
4544.74
4512.89
4508.55
4505.08
4497.60
4492.92
4280.97
4279.67
4231.86
4230.37
4224.17
4222.68
4216.19
4208.48
2315.86
1591.84
1128.34
1124.70
1121.65
1118.61
1114.94
H-2', H-6' (d) 8.02
H-3 (d) 7.75
H-4' (t) 7.58
H-3', H-5' (t) 7.52
A (d) 7.50
H-2" (d) 7.13
H-6" (dd) 7.04
H-5" (d) 7.02
CH2 (s) 3.86
H-2"', H-5"' (s) 2.65
H-3"', H-4"' (m) 1.87
2.00
1.00
0.98
3.08
1.02
1.02
1.00
2.09
4.02
4.15
8.05
8.00
7.75
7.60
7.55
7.50
7.15
7.05
7.00
3.85
2.75
2.70
2.65
2.60
2.55
1.90
1.85
f1 (ppm)
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00


5'
4'
6'
3'
1'
2'
1
2
3
O
6"
5"
1"
3"
2"
4"
5'
2'''
N
3"
5'''
4'''
OH
13

42

16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00

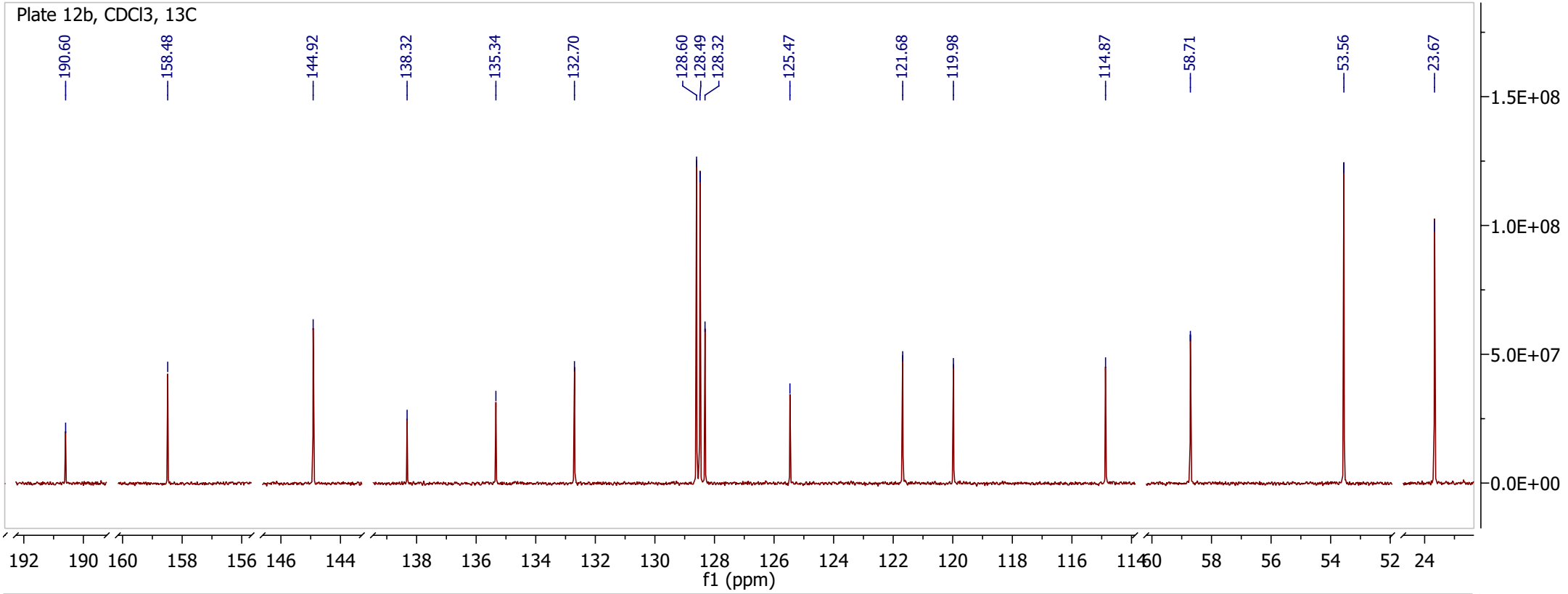
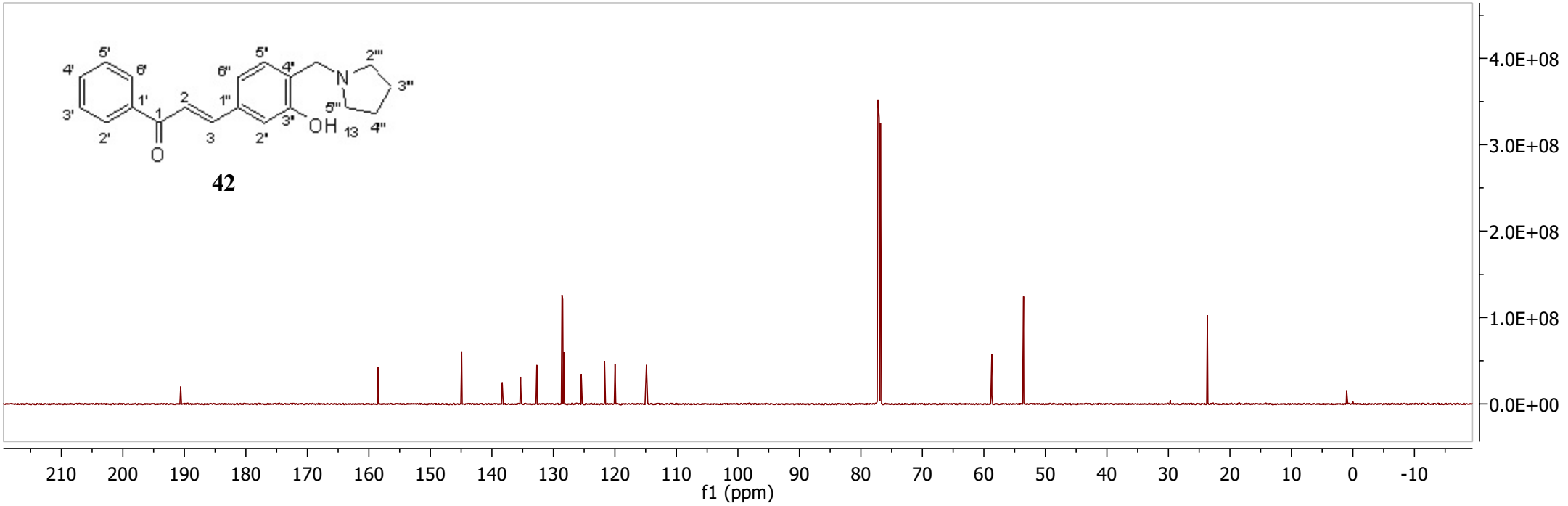


Plate 12b, CDCl3, 13C
190.60
158.48
144.92
138.32
135.34
132.70
128.60
128.49
128.32
125.47
121.68
119.98
114.87
58.71
53.56
23.67
1.5E+08
1.0E+08
5.0E+07
0.0E+00
192 190 160 158 156 146 144 138 136 134 132 130 128 126 124 122 120 118 116 114 60 58 56 54 52 24
f1 (ppm)


4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5'
4'
6'
3'
1'
2'
1
2
3
O
6"
5'
4'
1"
3'
OH
13
2"
4"
5"
N
2'''
3"

42

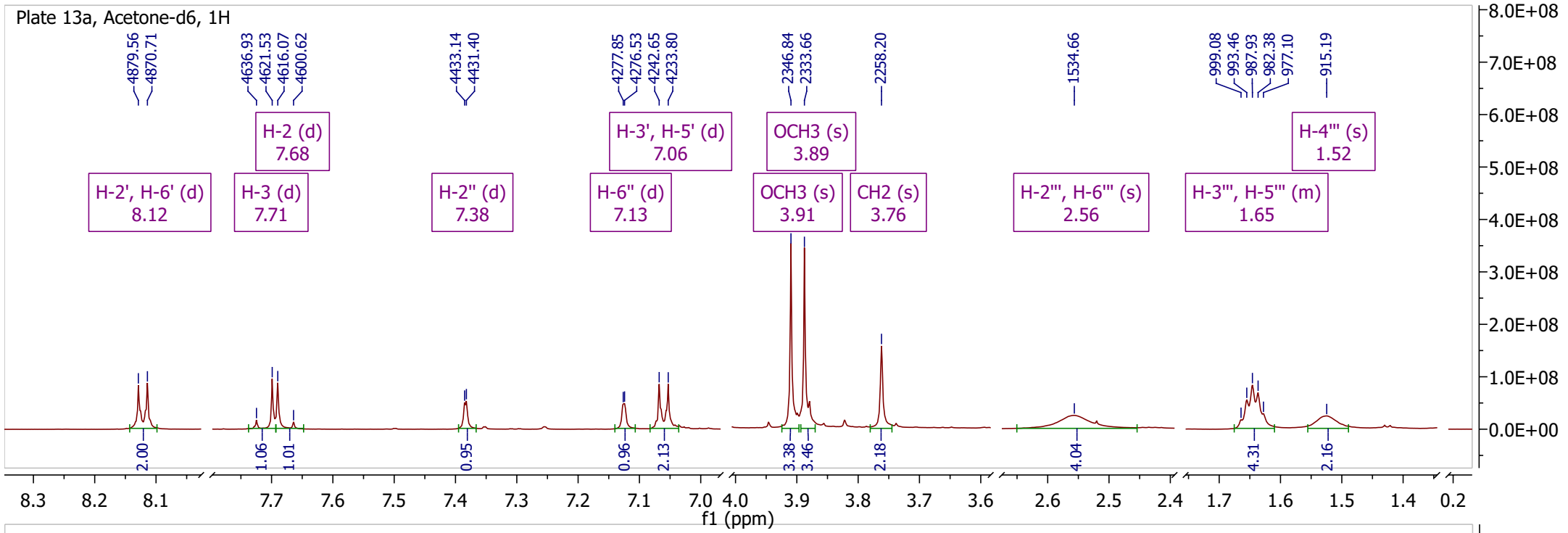
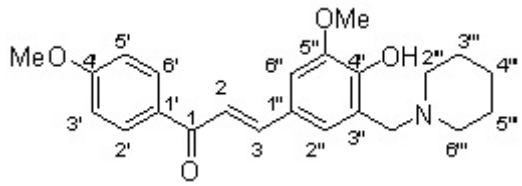


Plate 13a, Acetone-d6, 1H
4879.56
4870.71
4636.93
4621.53
4616.07
4600.62
4433.14
4431.40
4277.85
4276.53
4242.65
4233.80
2346.84
2333.66
2258.20
1534.66
999.08
993.46
987.93
982.38
977.10
915.19
H-2 (d) 7.68
H-3', H-5' (d) 7.06
OCH3 (s) 3.89
H-4''' (s) 1.52
H-2', H-6' (d) 8.12
H-3 (d) 7.71
H-2" (d) 7.38
H-6" (d) 7.13
OCH3 (s) 3.91
CH2 (s) 3.76
H-2''', H-6''' (s) 2.56
H-3''', H-5''' (m) 1.65
2.00
1.06
1.01
0.95
0.96
2.13
3.38
3.46
2.18
4.04
4.31
2.16
f1 (ppm)


MeO
OMe
OH
N
O

43

f1 (ppm)

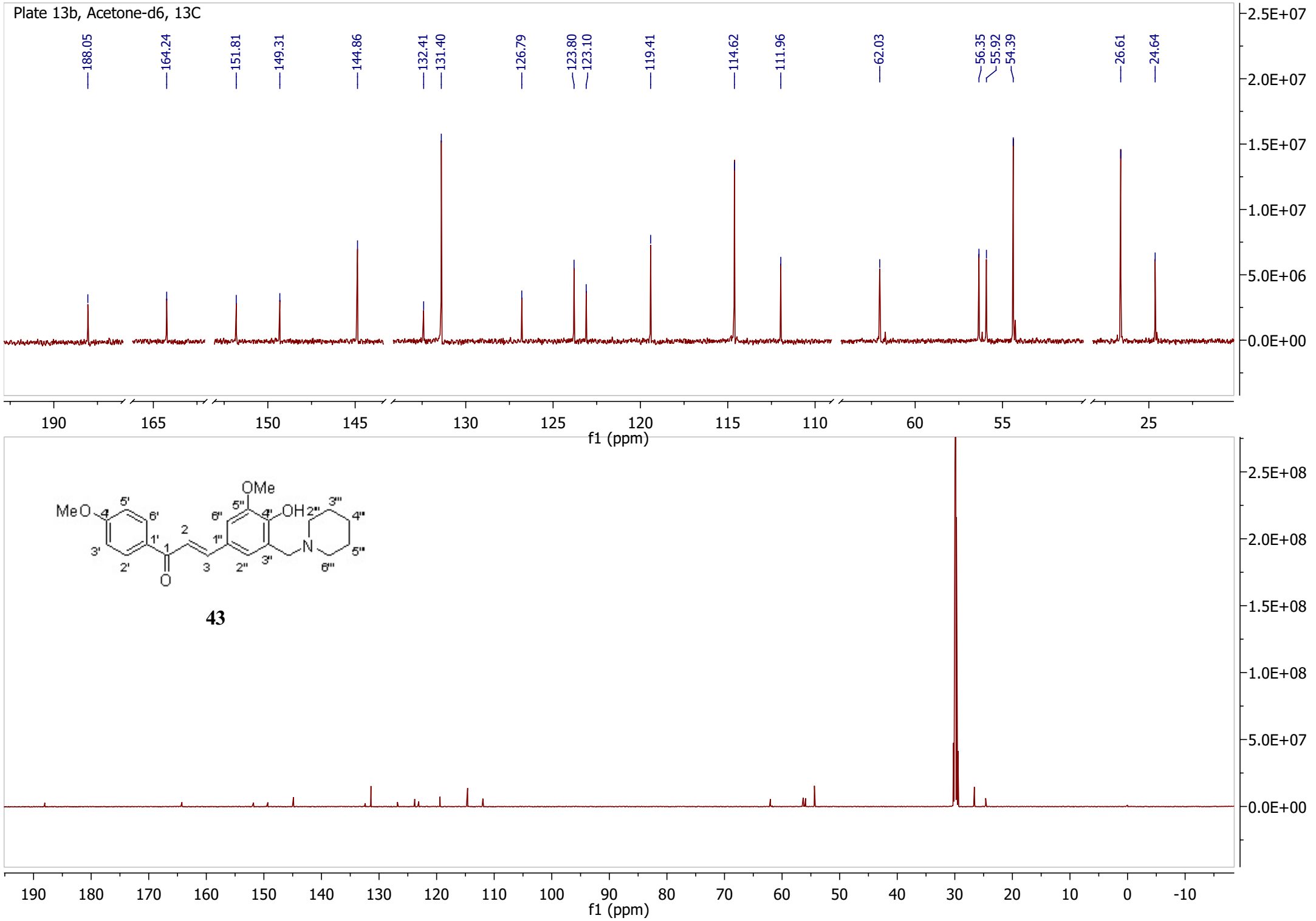


Plate 13b, Acetone-d6, 13C
188.05
164.24
151.81
149.31
144.86
132.41
131.40
126.79
123.80
123.10
119.41
114.62
111.96
62.03
56.35
55.92
54.39
26.61
24.64
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
190
165
150
145
130
125
120
115
110
60
55
25
f1 (ppm)
MeO
OMe
OH
N
O
43
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

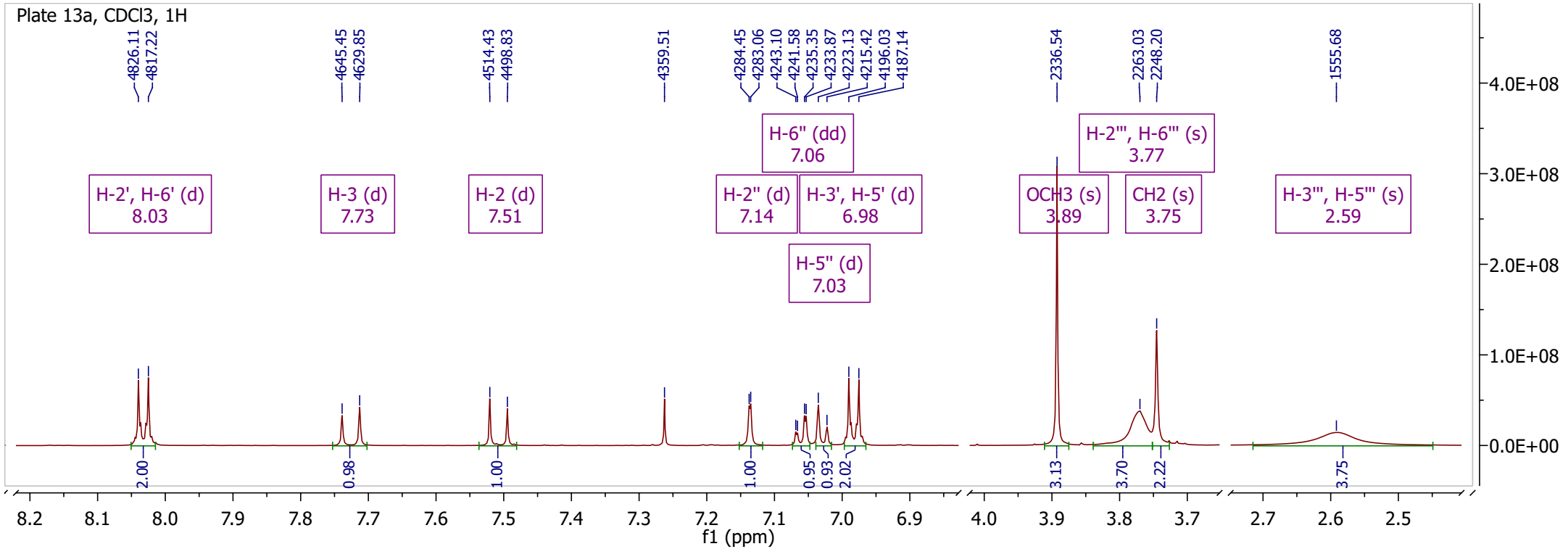
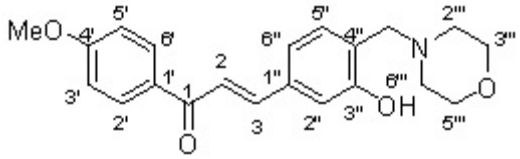


Plate 13a, CDCl3, 1H
4826.11
4817.22
4645.45
4629.85
4514.43
4498.83
4359.51
4284.45
4283.06
4243.10
4241.58
4235.35
4233.87
4223.13
4215.42
4196.03
4187.14
2336.54
2263.03
2248.20
1555.68
H-2', H-6' (d)
8.03
H-3 (d)
7.73
H-2 (d)
7.51
H-6" (dd)
7.06
H-2" (d)
7.14
H-3', H-5' (d)
6.98
H-5" (d)
7.03
OCH3 (s)
3.89
H-2"', H-6"' (s)
3.77
CH2 (s)
3.75
H-3"', H-5"' (s)
2.59
2.00
0.98
1.00
1.00
0.95
0.93
2.02
3.13
3.70
2.22
3.75
f1 (ppm)


MeO
OH
O
N

44

f1 (ppm)

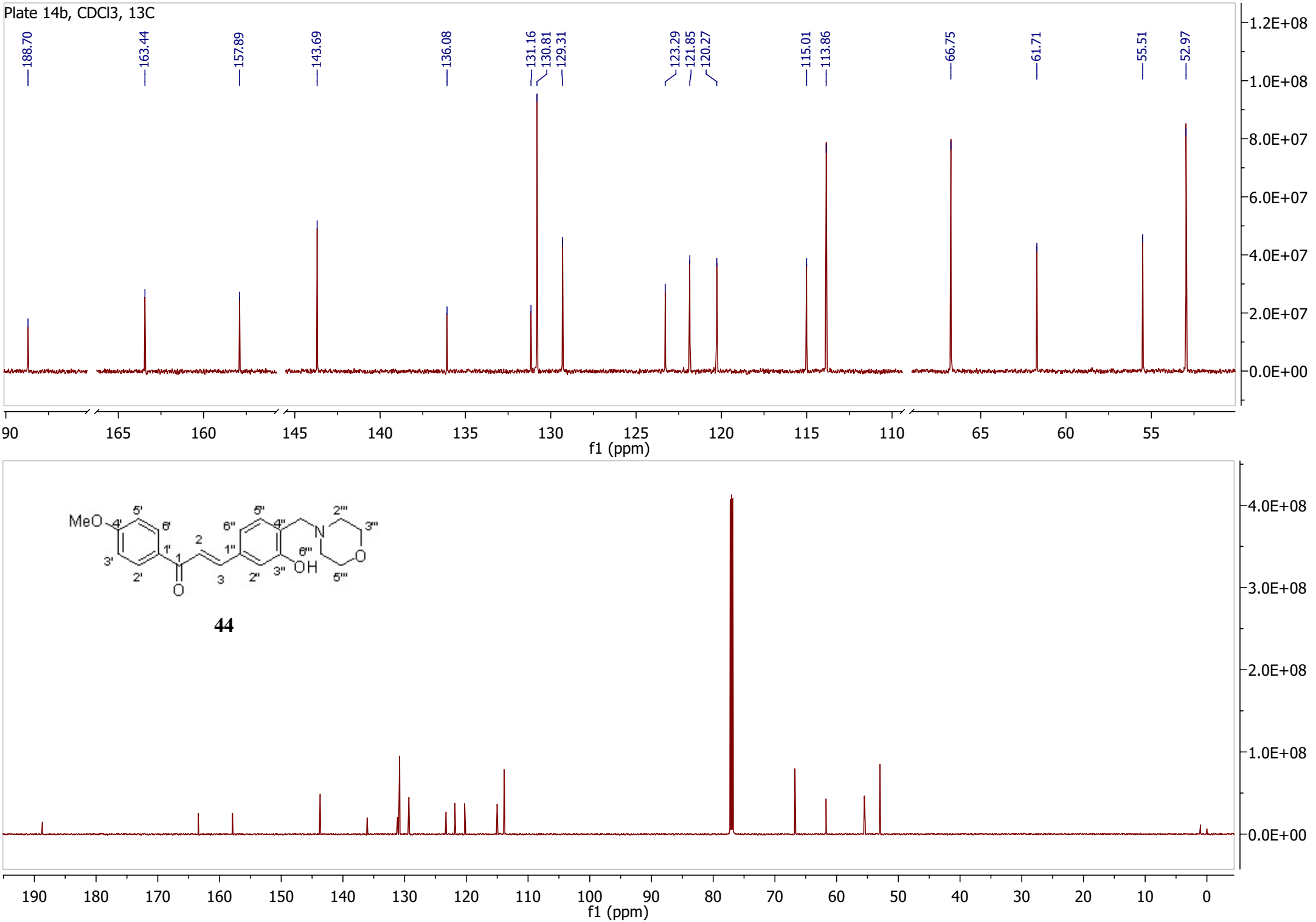


Plate 14b, CDCl3, 13C
188.70
163.44
157.89
143.69
136.08
131.16
130.81
129.31
123.29
121.85
120.27
115.01
113.86
66.75
61.71
55.51
52.97
f1 (ppm)
MeO
OH
O
N
44

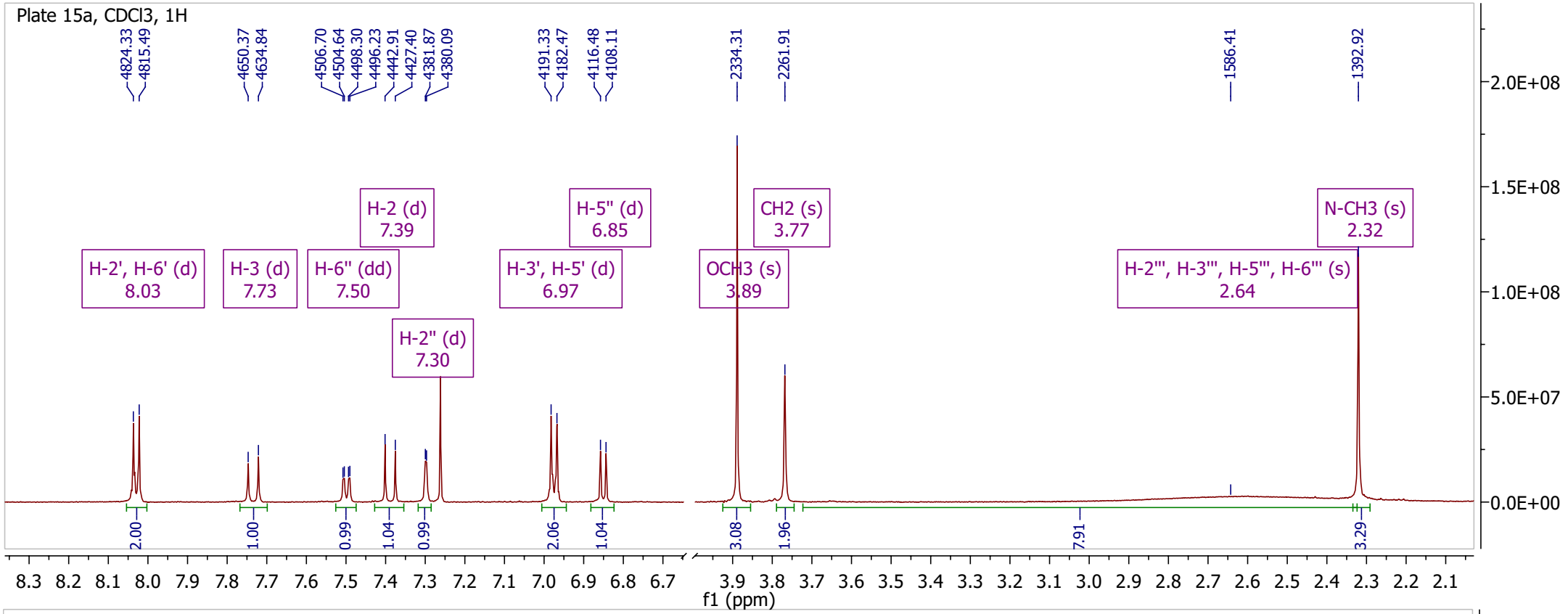
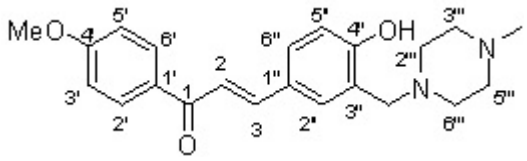


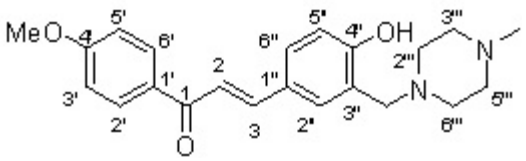
Plate 15a, CDCl3, 1H
4824.33
4815.49
4650.37
4634.84
4506.70
4504.64
4498.30
4496.23
4442.91
4427.40
4381.87
4380.09
4191.33
4182.47
4116.48
4108.11
2334.31
2261.91
1586.41
1392.92
H-2', H-6' (d) 8.03
H-3 (d) 7.73
H-6" (dd) 7.50
H-2 (d) 7.39
H-2" (d) 7.30
H-3', H-5' (d) 6.97
H-5" (d) 6.85
OCH3 (s) 3.89
CH2 (s) 3.77
H-2"', H-3"', H-5"', H-6"' (s) 2.64
N-CH3 (s) 2.32
2.00
1.00
0.99
1.04
0.99
2.06
1.04
3.08
1.96
7.91
3.29
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1
f1 (ppm)


MeO
OH
N
O

45

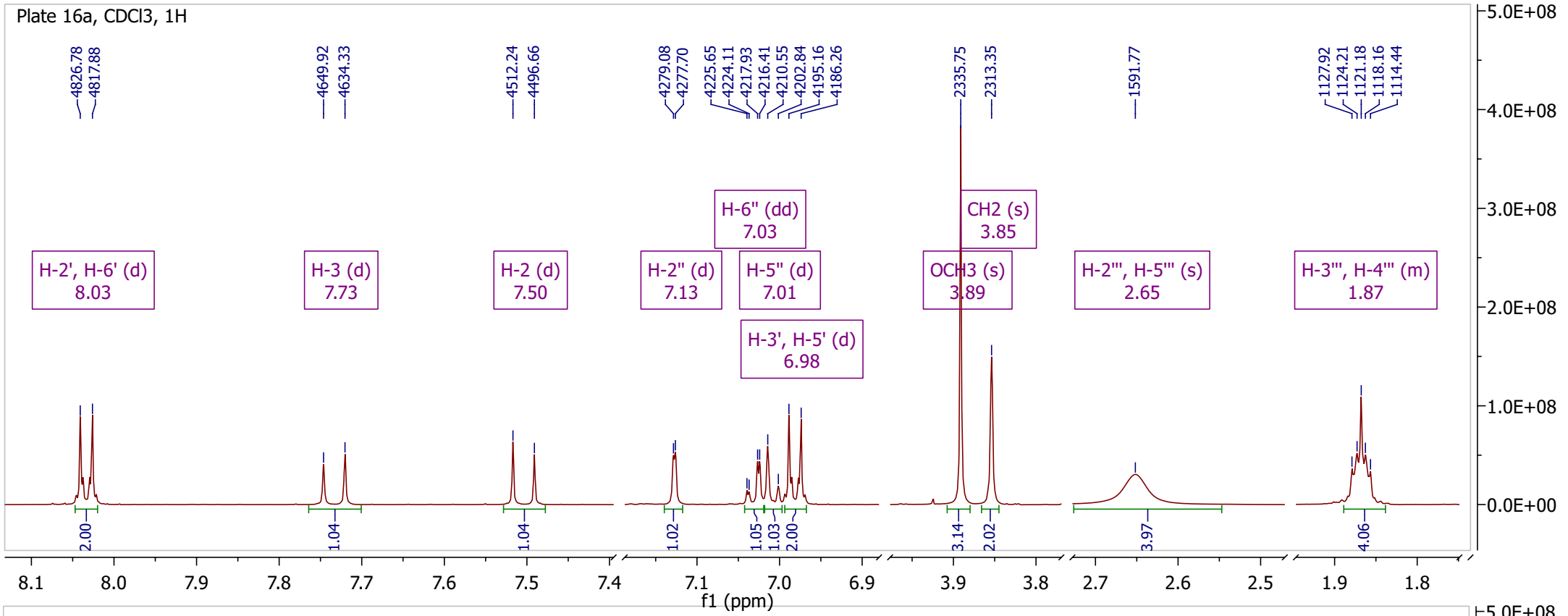
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

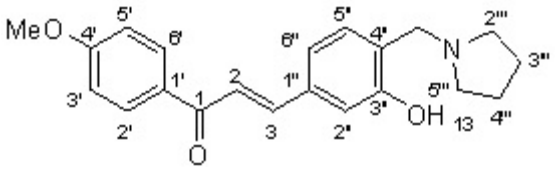
Plate 15b, CDCl3, 13C



45

Plate 16a, CDCl3, 1H





46

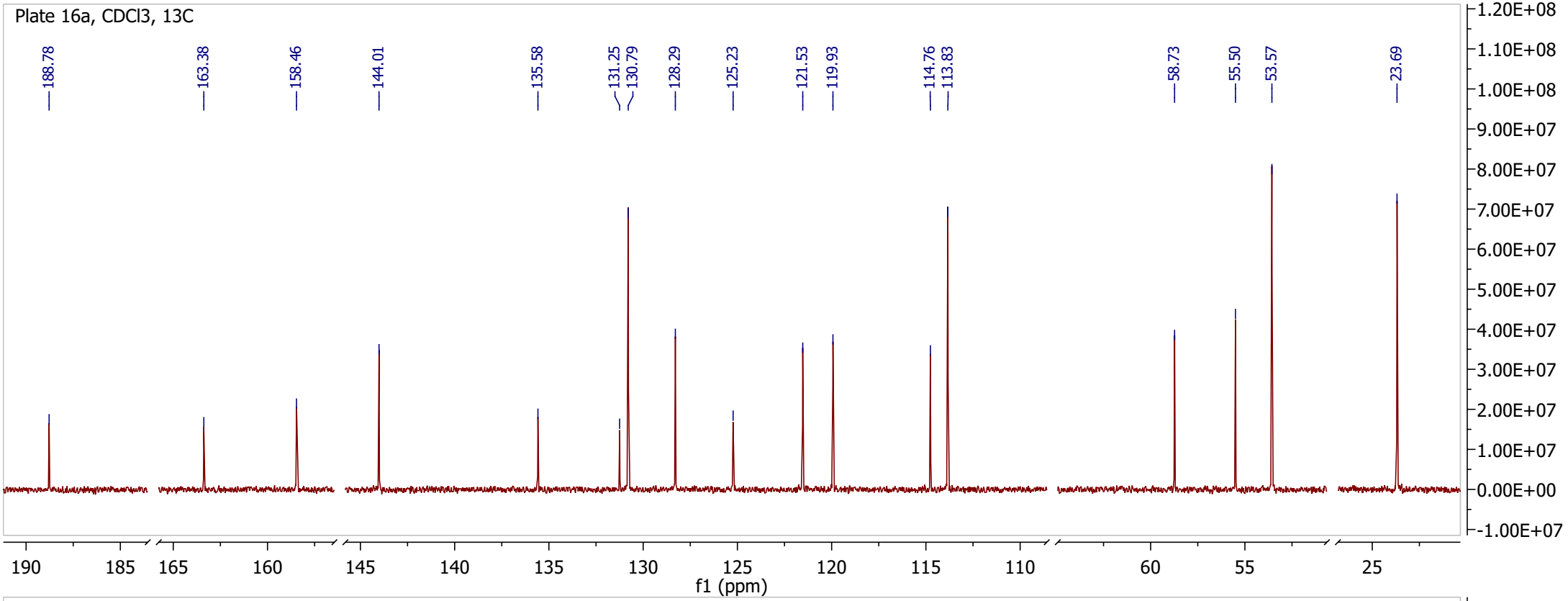
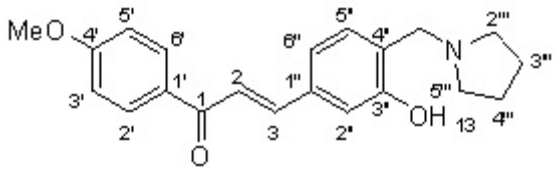


Plate 16a, CDCl3, 13C
188.78
163.38
158.46
144.01
135.58
131.25
130.79
128.29
125.23
121.53
119.93
114.76
113.83
58.73
55.50
53.57
23.69
f1 (ppm)


MeO
OH
O
N

46

f1 (ppm)

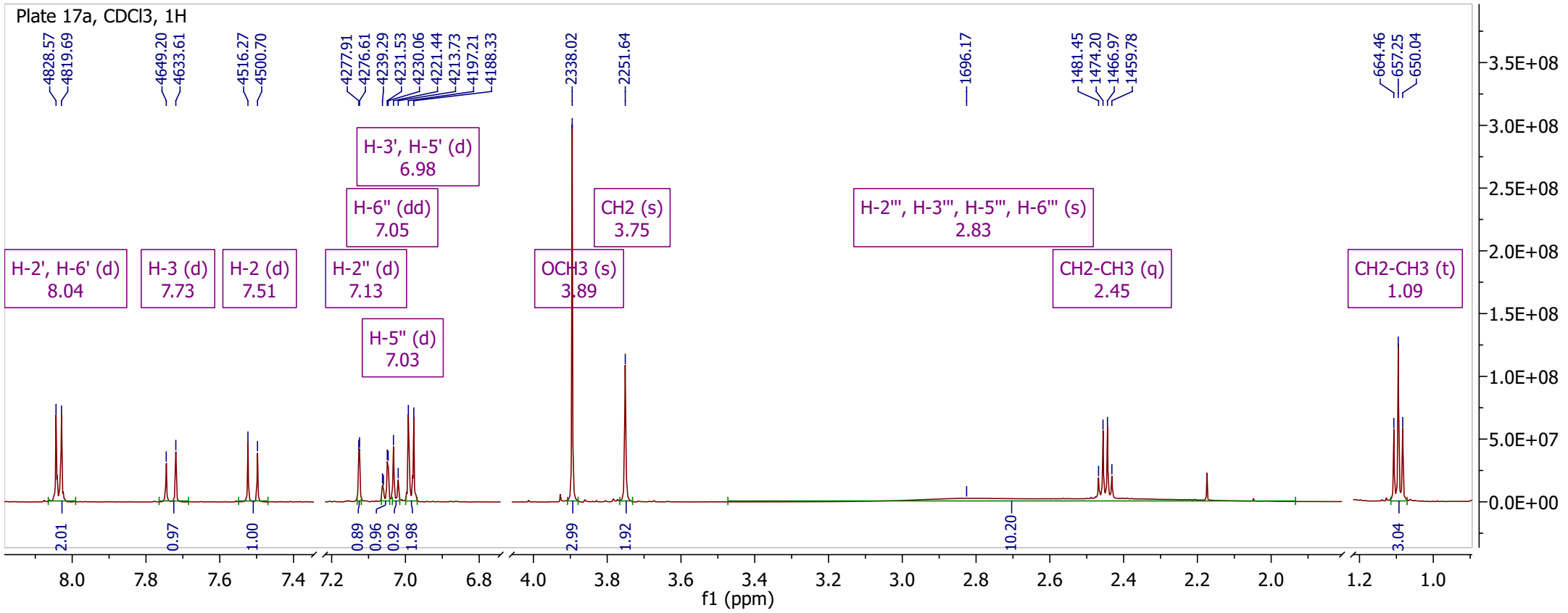
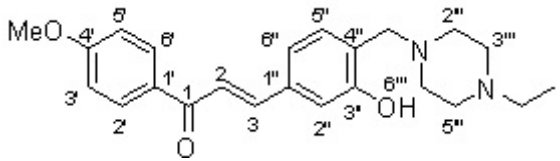


Plate 17a, CDCl3, 1H
4828.57
4819.69
4649.20
4633.61
4516.27
4500.70
4277.91
4276.61
4239.29
4231.53
4230.06
4221.44
4213.73
4197.21
4188.33
2338.02
2251.64
1696.17
1481.45
1474.20
1466.97
1459.78
664.46
657.25
650.04
H-3', H-5' (d)
6.98
H-6" (dd)
7.05
CH2 (s)
3.75
H-2"', H-3"', H-5"', H-6"' (s)
2.83
H-2', H-6' (d)
8.04
H-3 (d)
7.73
H-2 (d)
7.51
H-2" (d)
7.13
OCH3 (s)
3.89
CH2-CH3 (q)
2.45
CH2-CH3 (t)
1.09
H-5" (d)
7.03
2.01
0.97
1.00
0.89
0.96
0.92
1.98
2.99
1.92
10.20
3.04
f1 (ppm)


MeO
OH
O

47

f1 (ppm)

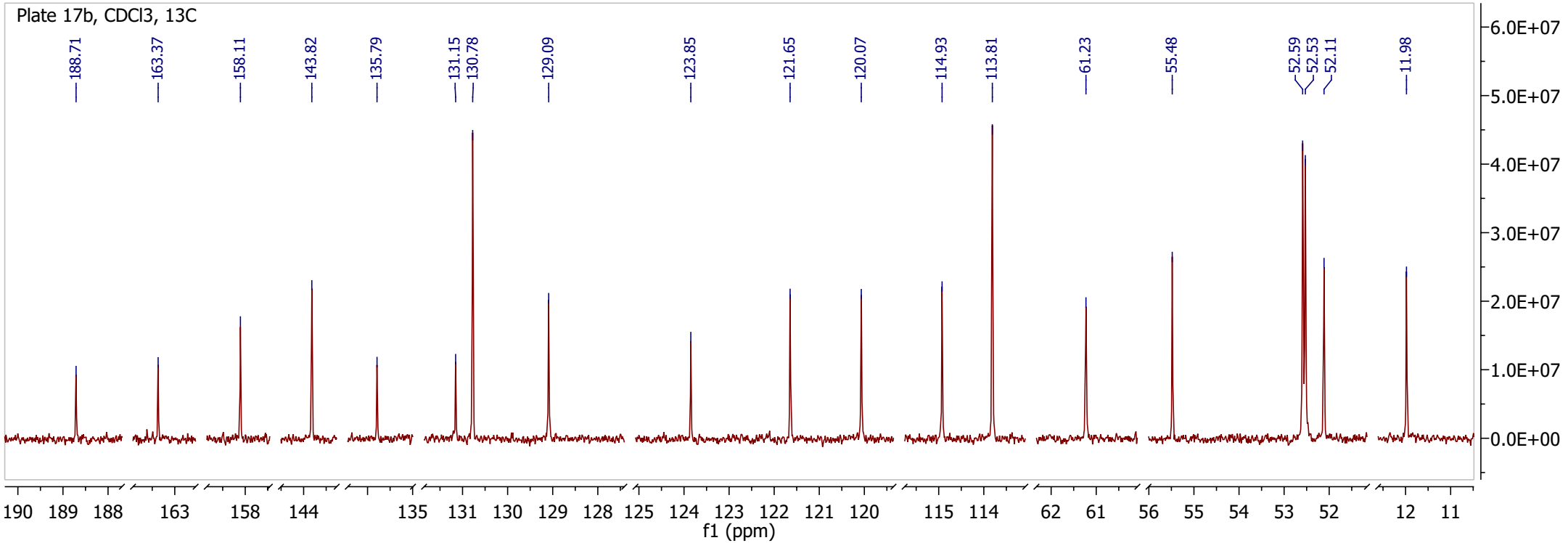
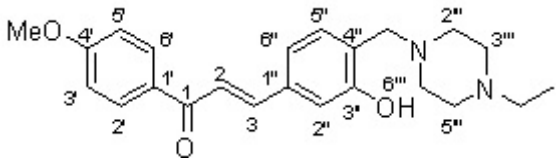


Plate 17b, CDCl3, 13C
188.71
163.37
158.11
143.82
135.79
131.15
130.78
129.09
123.85
121.65
120.07
114.93
113.81
61.23
55.48
52.59
52.53
52.11
11.98
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
190 189 188 163 158 144 135 131 130 129 128 125 124 123 122 121 120 115 114 62 61 56 55 54 53 52 12 11
f1 (ppm)


MeO
OH
O
N
N

47

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

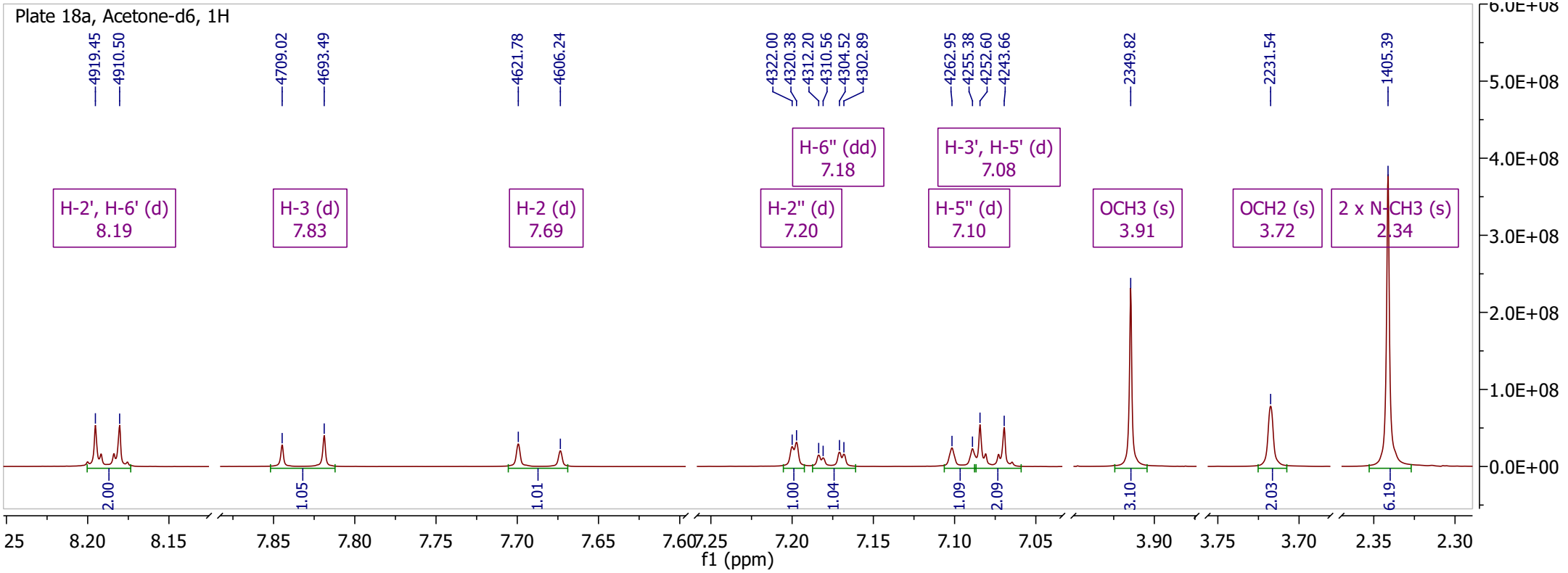
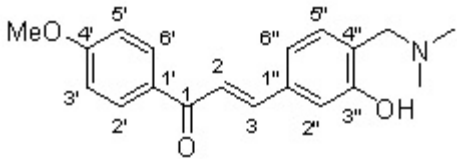


Plate 18a, Acetone-d6, 1H
4919.45
4910.50
4709.02
4693.49
4621.78
4606.24
4322.00
4320.38
4312.20
4310.56
4304.52
4302.89
4262.95
4255.38
4252.60
4243.66
2349.82
2231.54
1405.39
H-2', H-6' (d) 8.19
H-3 (d) 7.83
H-2 (d) 7.69
H-6" (dd) 7.18
H-2" (d) 7.20
H-3', H-5' (d) 7.08
H-5" (d) 7.10
OCH3 (s) 3.91
OCH2 (s) 3.72
2 x N-CH3 (s) 2.34
2.00
1.05
1.01
1.00
1.04
1.09
2.09
3.10
2.03
6.19
f1 (ppm)


MeO
5'
4'
6'
1'
2
1
3'
2'
3
O
6"
5"
4"
1"
3"
2"
N
OH

48

f1 (ppm)

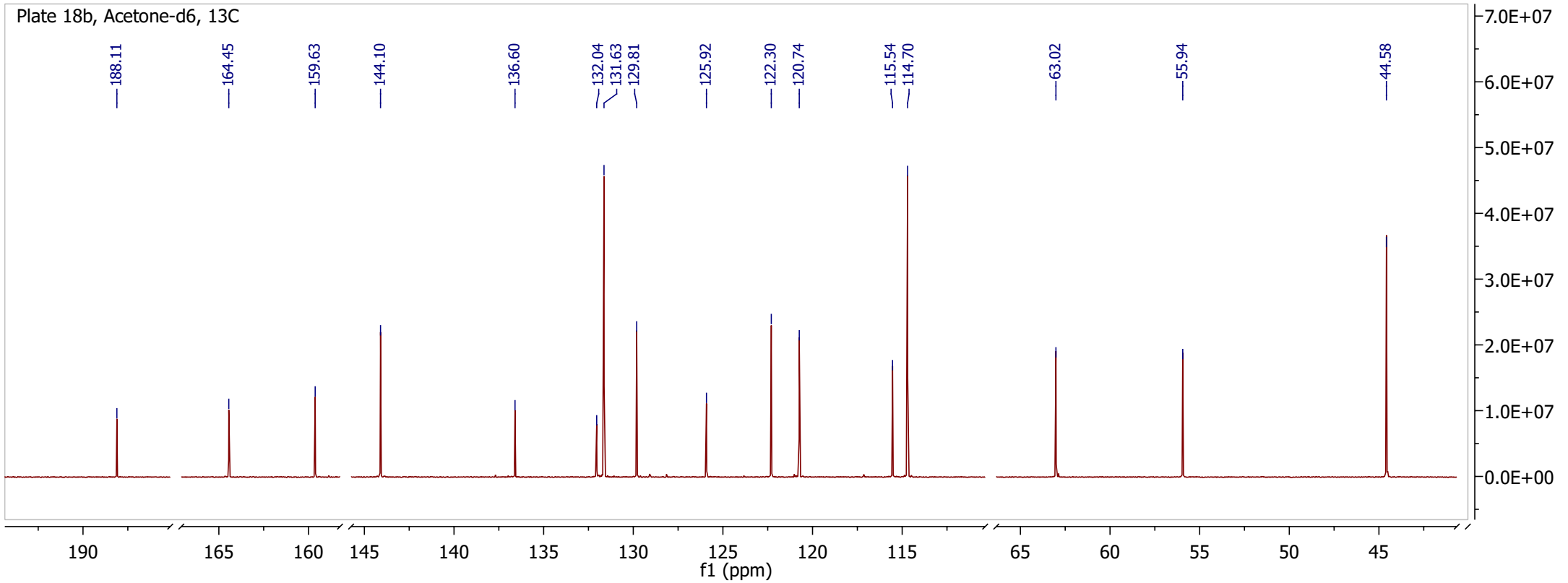
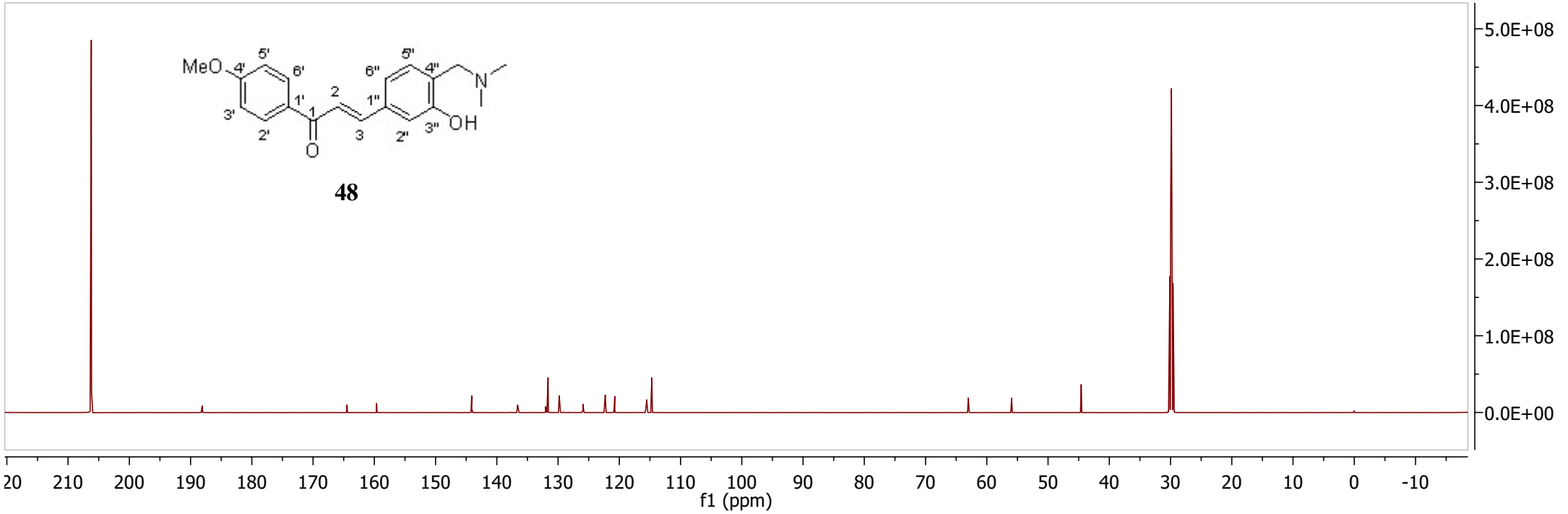


Plate 18b, Acetone-d6, 13C
188.11
164.45
159.63
144.10
136.60
132.04
131.63
129.81
125.92
122.30
120.74
115.54
114.70
63.02
55.94
44.58
7.0E+07
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
190
165
160
145
140
135
130
125
120
115
65
60
55
50
45
f1 (ppm)


MeO
OH
N
O
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
f1 (ppm)

48

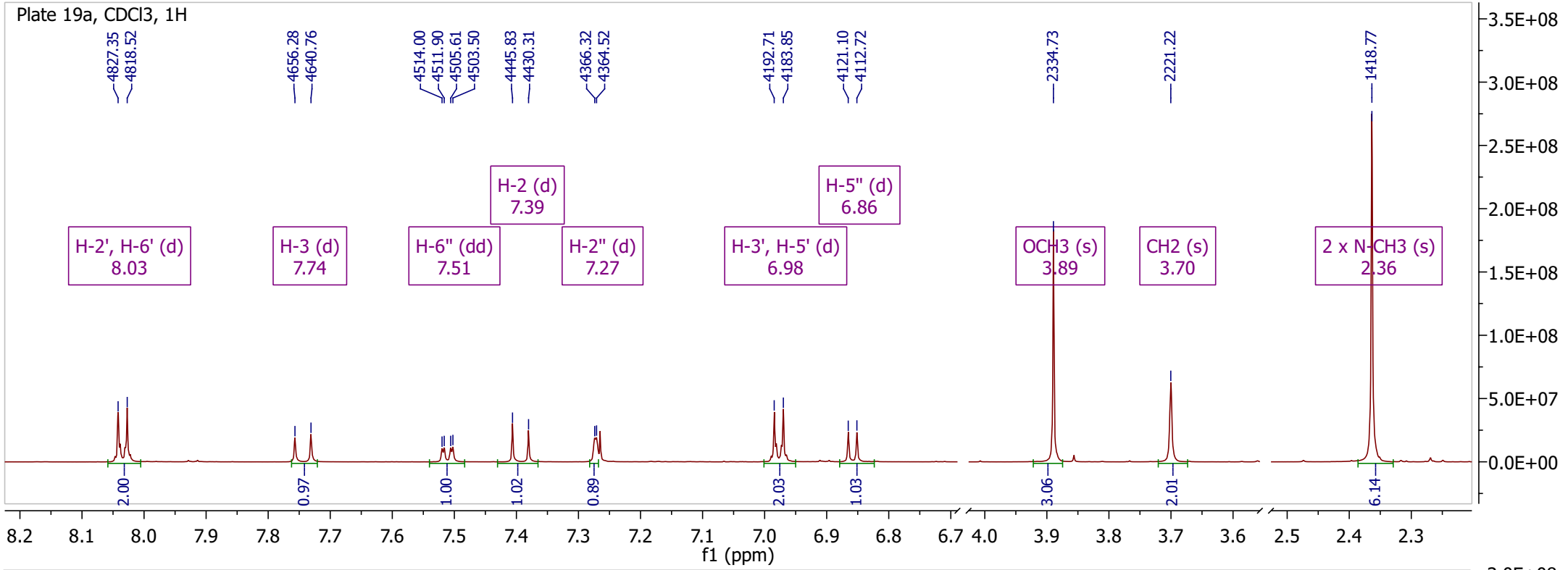
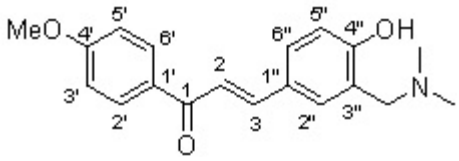


Plate 19a, CDCl3, 1H
4827.35
4818.52
4656.28
4640.76
4514.00
4511.90
4505.61
4503.50
4445.83
4430.31
4366.32
4364.52
4192.71
4183.85
4121.10
4112.72
2334.73
2221.22
1418.77
H-2', H-6' (d) 8.03
H-3 (d) 7.74
H-6" (dd) 7.51
H-2 (d) 7.39
H-2" (d) 7.27
H-3', H-5' (d) 6.98
H-5" (d) 6.86
OCH3 (s) 3.89
CH2 (s) 3.70
2 x N-CH3 (s) 2.36
2.00
0.97
1.00
1.02
0.89
2.03
1.03
3.06
2.01
6.14
f1 (ppm)


MeO
OH
N
O

49

f1 (ppm)

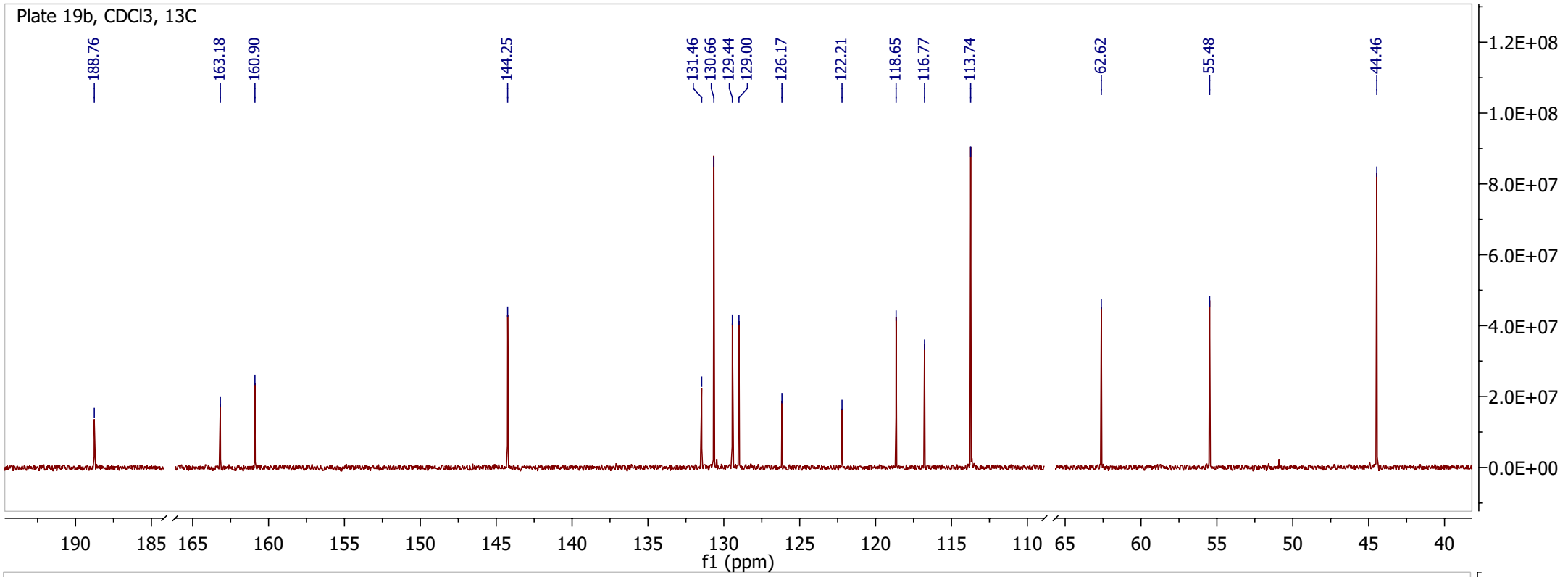
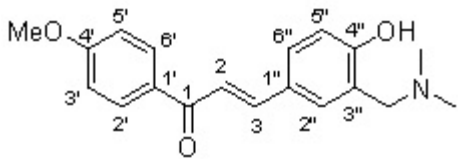


Plate 19b, CDCl3, 13C
188.76
163.18
160.90
144.25
131.46
130.66
129.44
129.00
126.17
122.21
118.65
116.77
113.74
62.62
55.48
44.46
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
190
185
165
160
155
150
145
140
135
130
125
120
115
110
65
60
55
50
45
40
f1 (ppm)


MeO
4'
5'
6'
1'
2
1"
6"
5'
4"
OH
3'
2'
1
3
2'
3"
N
O

49

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

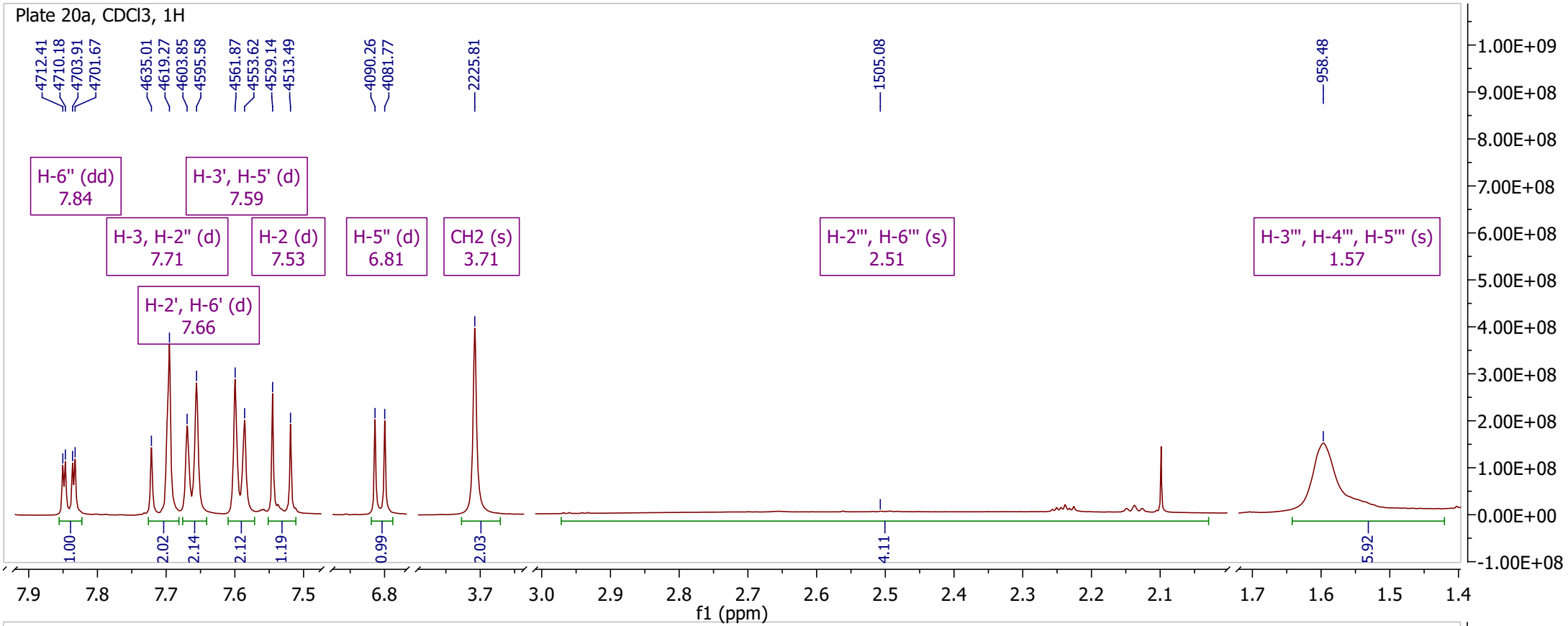
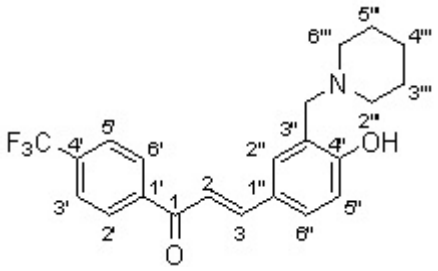


Plate 20a, CDCl3, 1H
4712.41
4710.18
4703.91
4701.67
4635.01
4619.27
4603.85
4595.58
4561.87
4553.62
4529.14
4513.49
4090.26
4081.77
2225.81
1505.08
958.48
H-6'' (dd)
7.84
H-3', H-5' (d)
7.59
H-3, H-2'' (d)
7.71
H-2 (d)
7.53
H-5'' (d)
6.81
CH2 (s)
3.71
H-2''', H-6''' (s)
2.51
H-3''', H-4''', H-5''' (s)
1.57
H-2', H-6' (d)
7.66
1.00
2.02
2.14
2.12
1.19
0.99
2.03
4.11
5.92
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
-1.00E+08
7.9
7.8
7.7
7.6
7.5
6.8
3.7
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
1.7
1.6
1.5
1.4
f1 (ppm)


F3C
OH
N
O

50

2.5E+09
2.0E+09
1.5E+09
1.0E+09
5.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

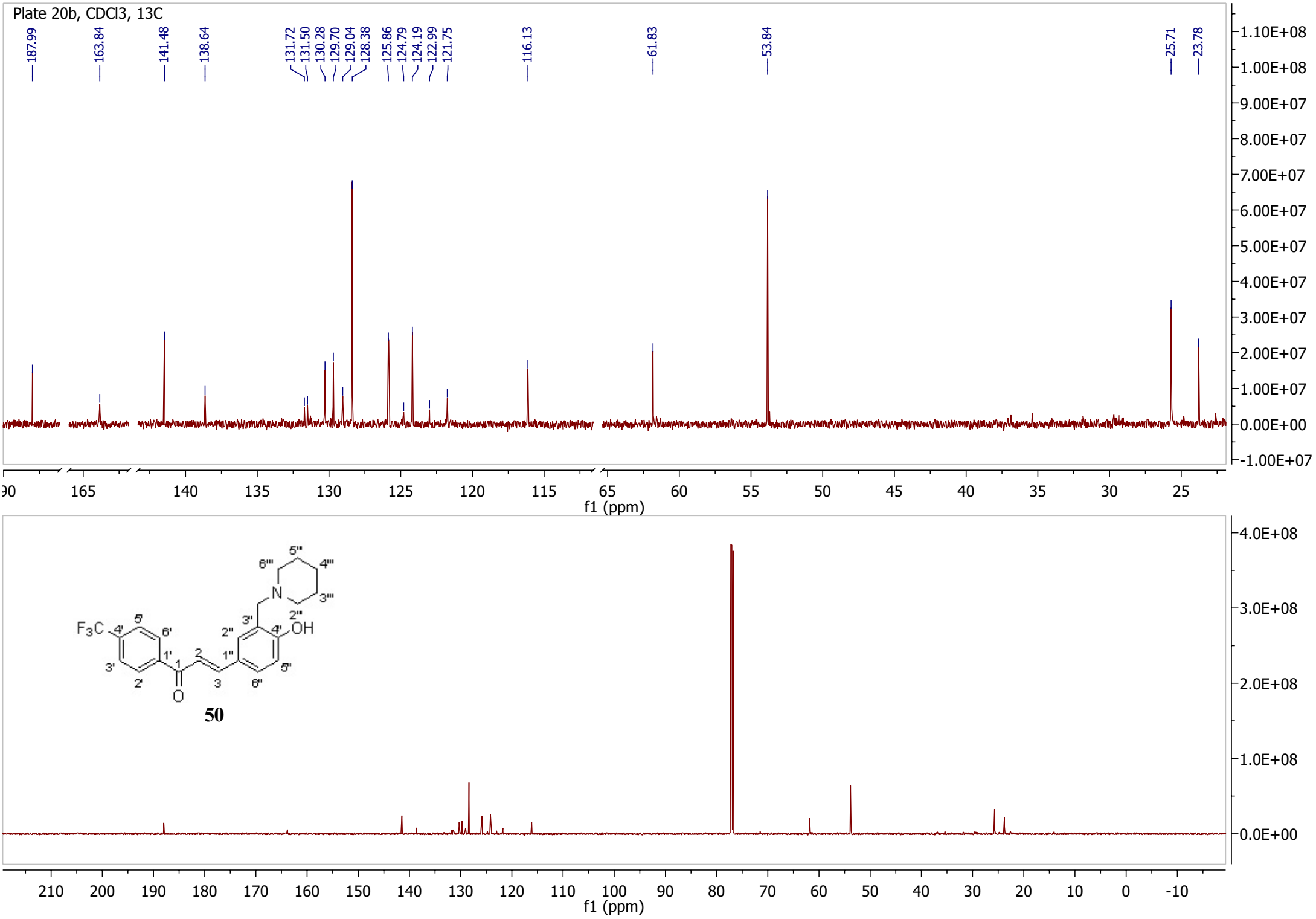


Plate 20b, CDCl3, 13C
187.99
163.84
141.48
138.64
131.72
131.50
130.28
129.70
129.04
128.38
125.86
124.79
124.19
122.99
121.75
116.13
61.83
53.84
25.71
23.78
f1 (ppm)
f1 (ppm)
50

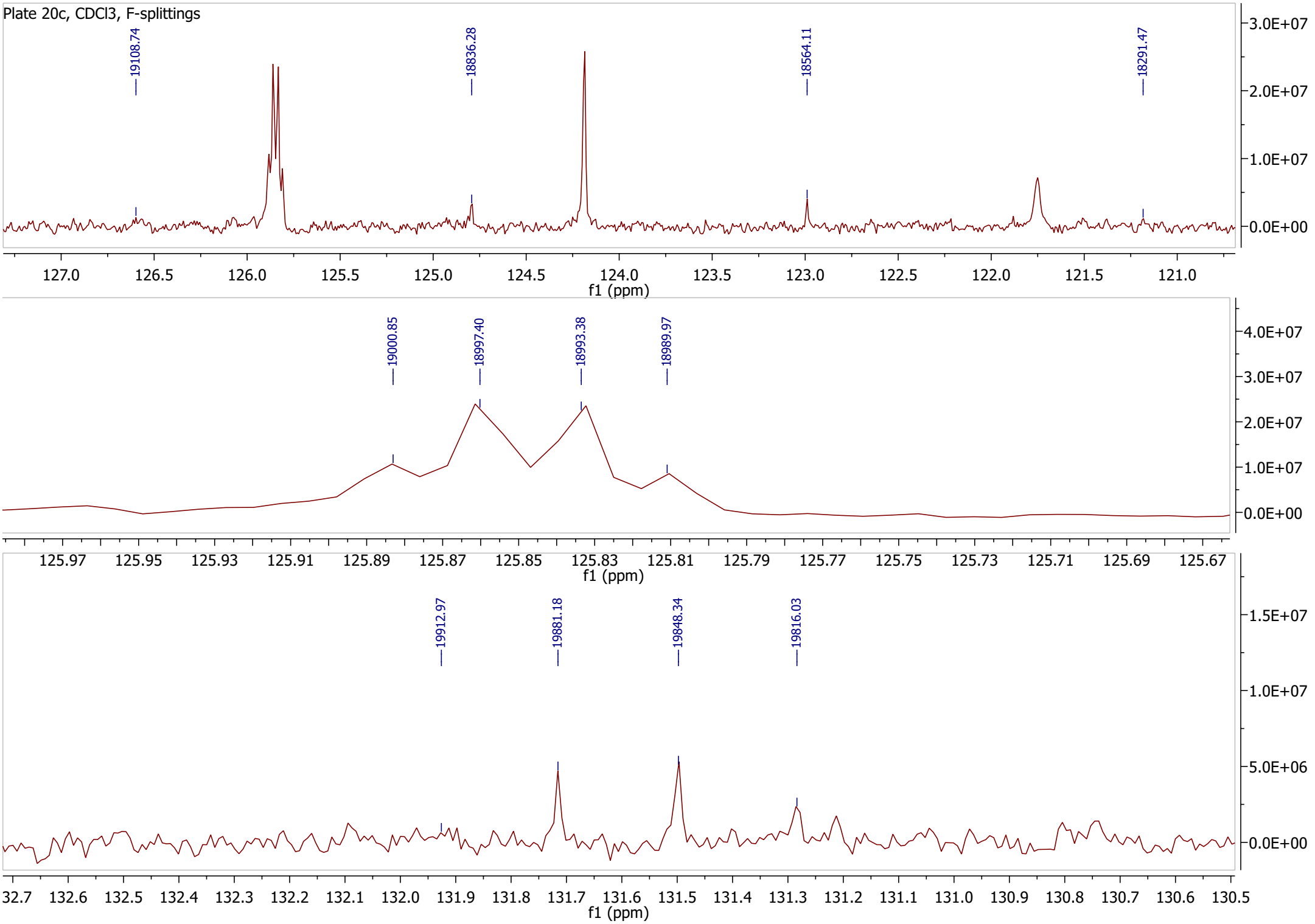


Plate 20c, CDCl3, F-splittings
19108.74
18836.28
18564.11
18291.47
3.0E+07
2.0E+07
1.0E+07
0.0E+00
127.0
126.5
126.0
125.5
125.0
124.5
124.0
123.5
123.0
122.5
122.0
121.5
121.0
f1 (ppm)
19000.85
18997.40
18993.38
18989.97
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
125.97
125.95
125.93
125.91
125.89
125.87
125.85
125.83
125.81
125.79
125.77
125.75
125.73
125.71
125.69
125.67
f1 (ppm)
19912.97
19881.18
19848.34
19816.03
1.5E+07
1.0E+07
5.0E+06
0.0E+00
32.7
132.6
132.5
132.4
132.3
132.2
132.1
132.0
131.9
131.8
131.7
131.6
131.5
131.4
131.3
131.2
131.1
131.0
130.9
130.8
130.7
130.6
130.5
f1 (ppm)

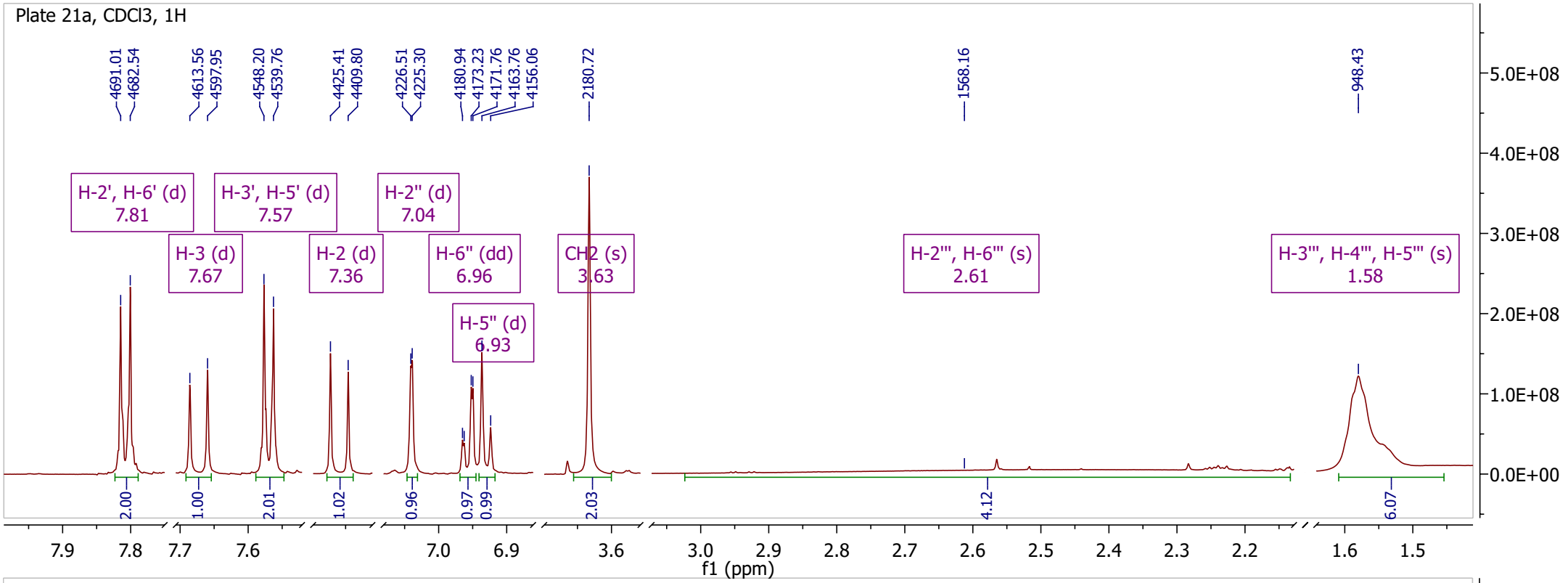
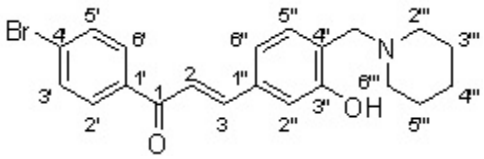


Plate 21a, CDCl3, 1H
4691.01
4682.54
4613.56
4597.95
4548.20
4539.76
4425.41
4409.80
4226.51
4225.30
4180.94
4173.23
4171.76
4163.76
4156.06
2180.72
1568.16
948.43
H-2', H-6' (d) 7.81
H-3', H-5' (d) 7.57
H-2" (d) 7.04
H-3 (d) 7.67
H-2 (d) 7.36
H-6" (dd) 6.96
H-5" (d) 6.93
CH2 (s) 3.63
H-2"', H-6"' (s) 2.61
H-3"', H-4"', H-5"' (s) 1.58
2.00
1.00
2.01
1.02
0.96
0.97
0.99
2.03
4.12
6.07
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.9
7.8
7.7
7.6
7.0
6.9
3.6
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
1.6
1.5
f1 (ppm)


Br
OH
O
N

51

8.0E+08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

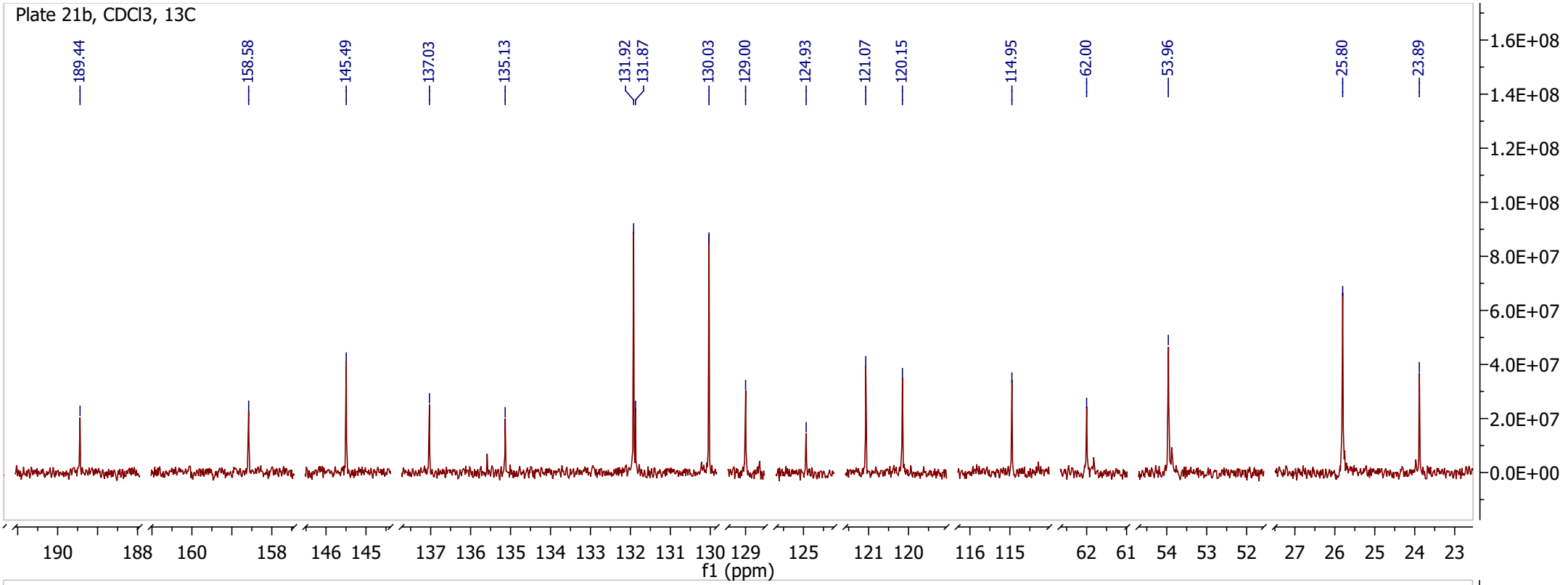
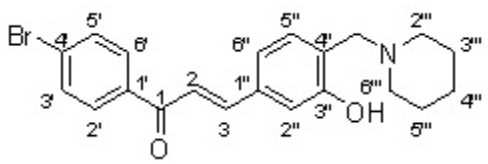


Plate 21b, CDCl3, 13C
189.44
158.58
145.49
137.03
135.13
131.92
131.87
130.03
129.00
124.93
121.07
120.15
114.95
62.00
53.96
25.80
23.89
1.6E+08
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
190 188 160 158 146 145 137 136 135 134 133 132 131 130 129 125 121 120 116 115 62 61 54 53 52 27 26 25 24 23
f1 (ppm)


Br
5'
4'
6'
3'
1'
2'
1
2
3
O
6"
5"
4'
1"
3"
2"
N
2"
3"
6"'
OH
4"
5"

51

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

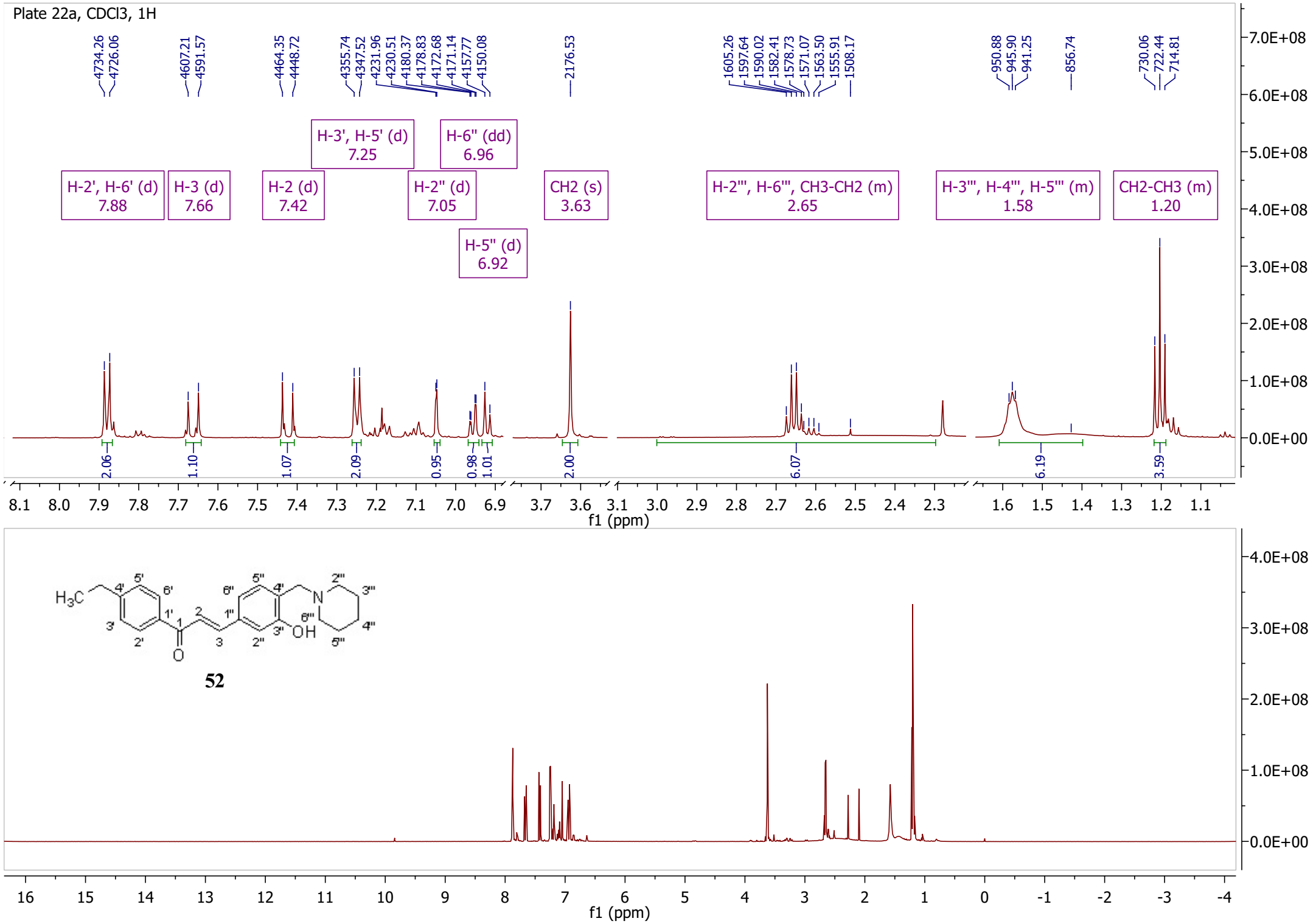


Plate 22a, CDCl3, 1H
4734.26
4726.06
4607.21
4591.57
4464.35
4448.72
4355.74
4347.52
4231.96
4230.51
4180.37
4178.83
4172.68
4171.14
4157.77
4150.08
2176.53
1605.26
1597.64
1590.02
1582.41
1578.73
1571.07
1563.50
1555.91
1508.17
950.88
945.90
941.25
856.74
730.06
722.44
714.81
H-2', H-6' (d)
7.88
H-3 (d)
7.66
H-2 (d)
7.42
H-3', H-5' (d)
7.25
H-2" (d)
7.05
H-6" (dd)
6.96
H-5" (d)
6.92
CH2 (s)
3.63
H-2"', H-6"', CH3-CH2 (m)
2.65
H-3"', H-4"', H-5"' (m)
1.58
CH2-CH3 (m)
1.20
2.06
1.10
1.07
2.09
0.95
0.98
1.01
2.00
6.07
6.19
3.59
f1 (ppm)
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
H3C
OH
O
52
f1 (ppm)
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00

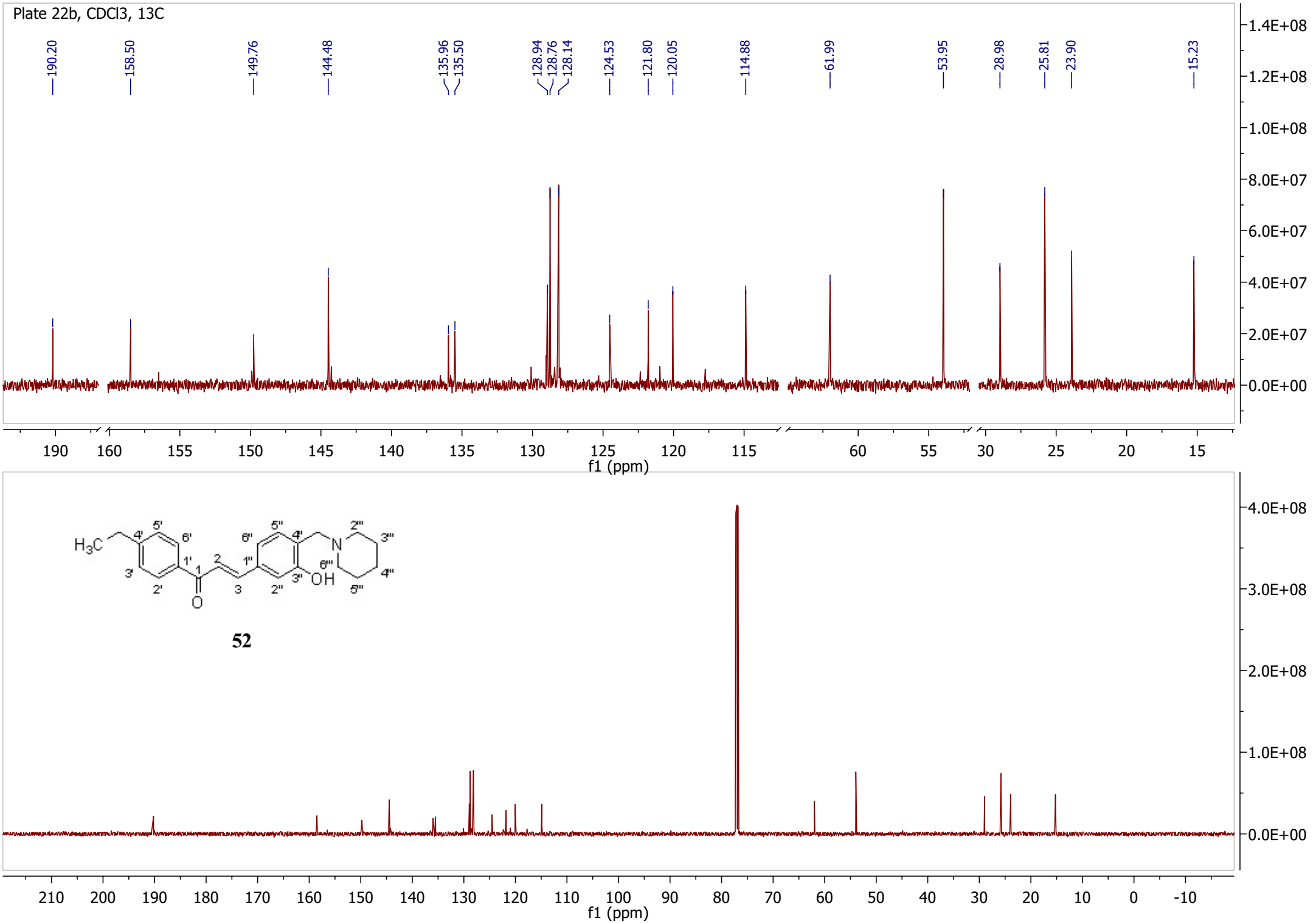


Plate 22b, CDCl3, 13C
190.20
158.50
149.76
144.48
135.96
135.50
128.94
128.76
128.14
124.53
121.80
120.05
114.88
61.99
53.95
28.98
25.81
23.90
15.23
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
190 160 155 150 145 140 135 130 125 120 115 60 55 30 25 20 15
f1 (ppm)
H3C
OH
O
N
52
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

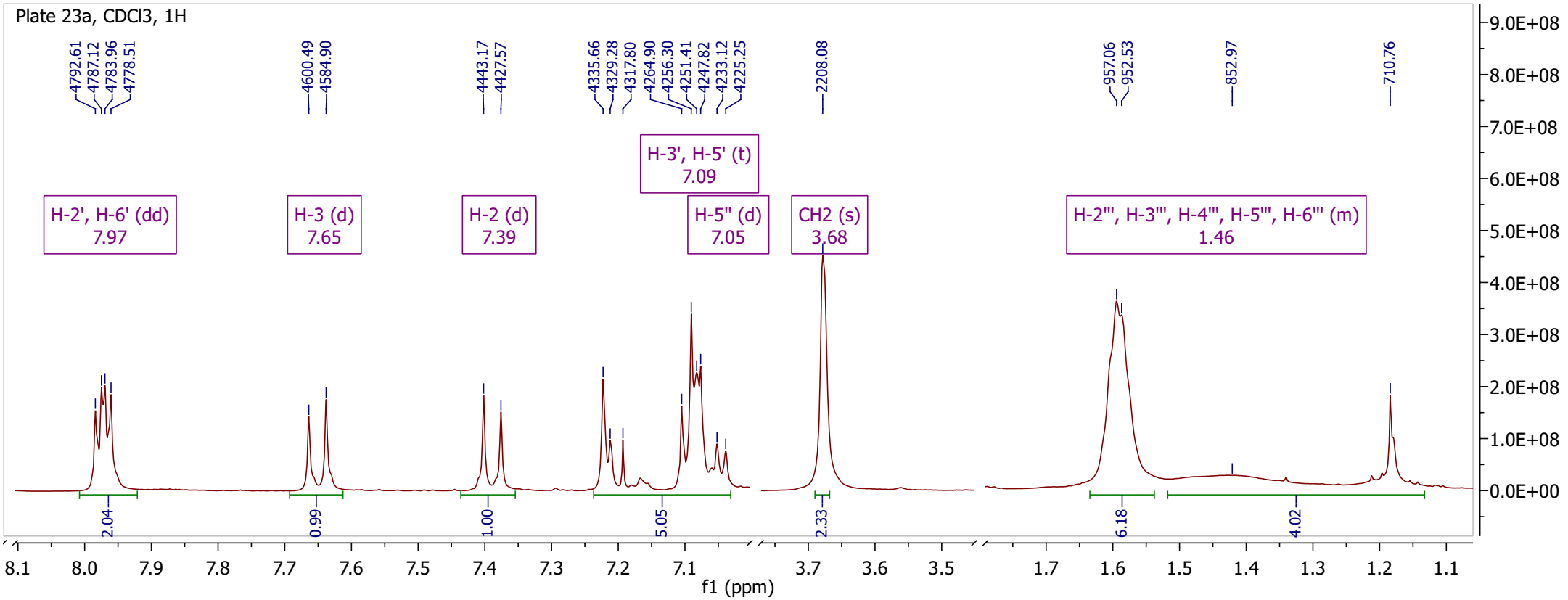
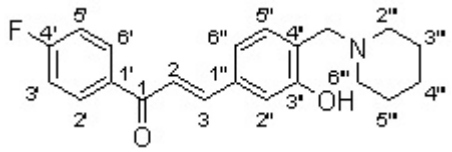


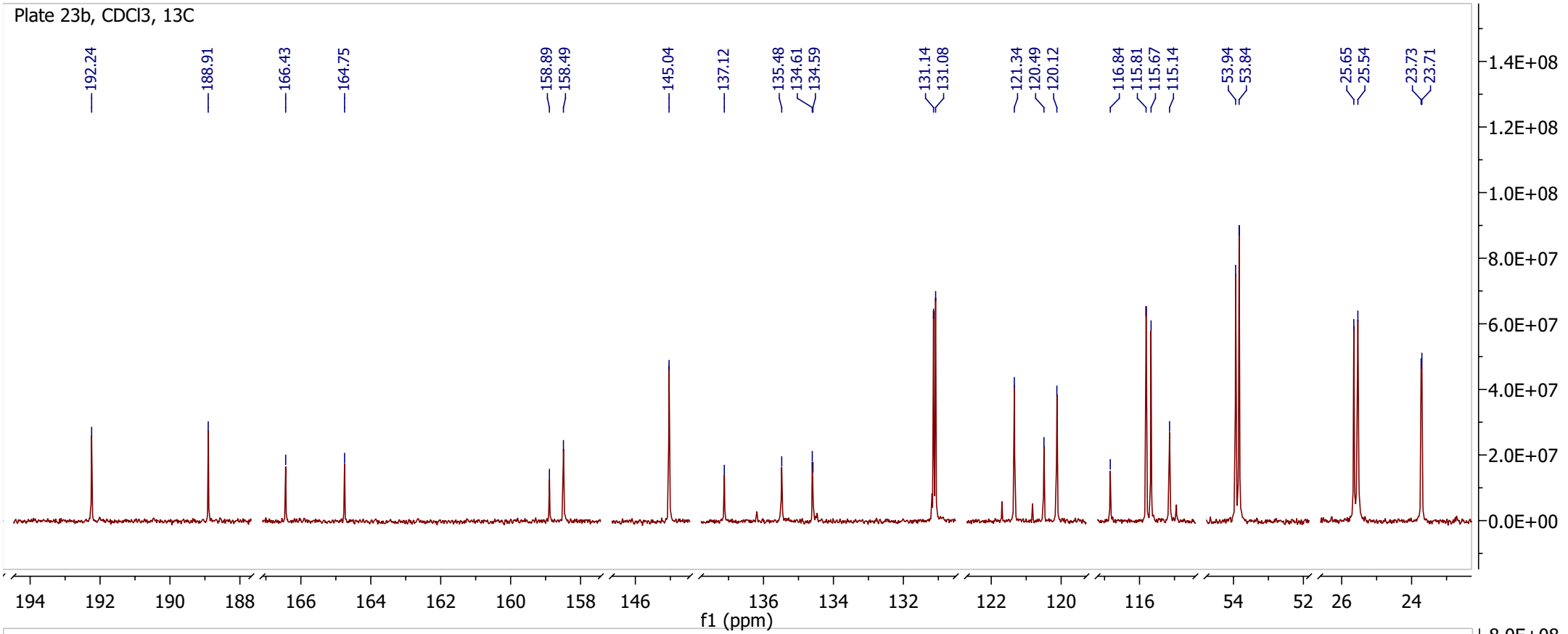
Plate 23a, CDCl3, 1H
4792.61
4787.12
4783.96
4778.51
4600.49
4584.90
4443.17
4427.57
4335.66
4329.28
4317.80
4264.90
4256.30
4251.41
4247.82
4233.12
4225.25
2208.08
957.06
952.53
852.97
710.76
H-2', H-6' (dd)
7.97
H-3 (d)
7.65
H-2 (d)
7.39
H-3', H-5' (t)
7.09
H-5" (d)
7.05
CH2 (s)
3.68
H-2"', H-3"', H-4"', H-5"', H-6"' (m)
1.46
2.04
0.99
1.00
5.05
2.33
6.18
4.02
f1 (ppm)

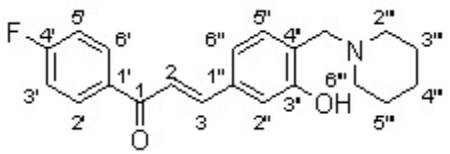

F
OH
N
O

53

f1 (ppm)

Plate 23b, CDCl3, 13C





53

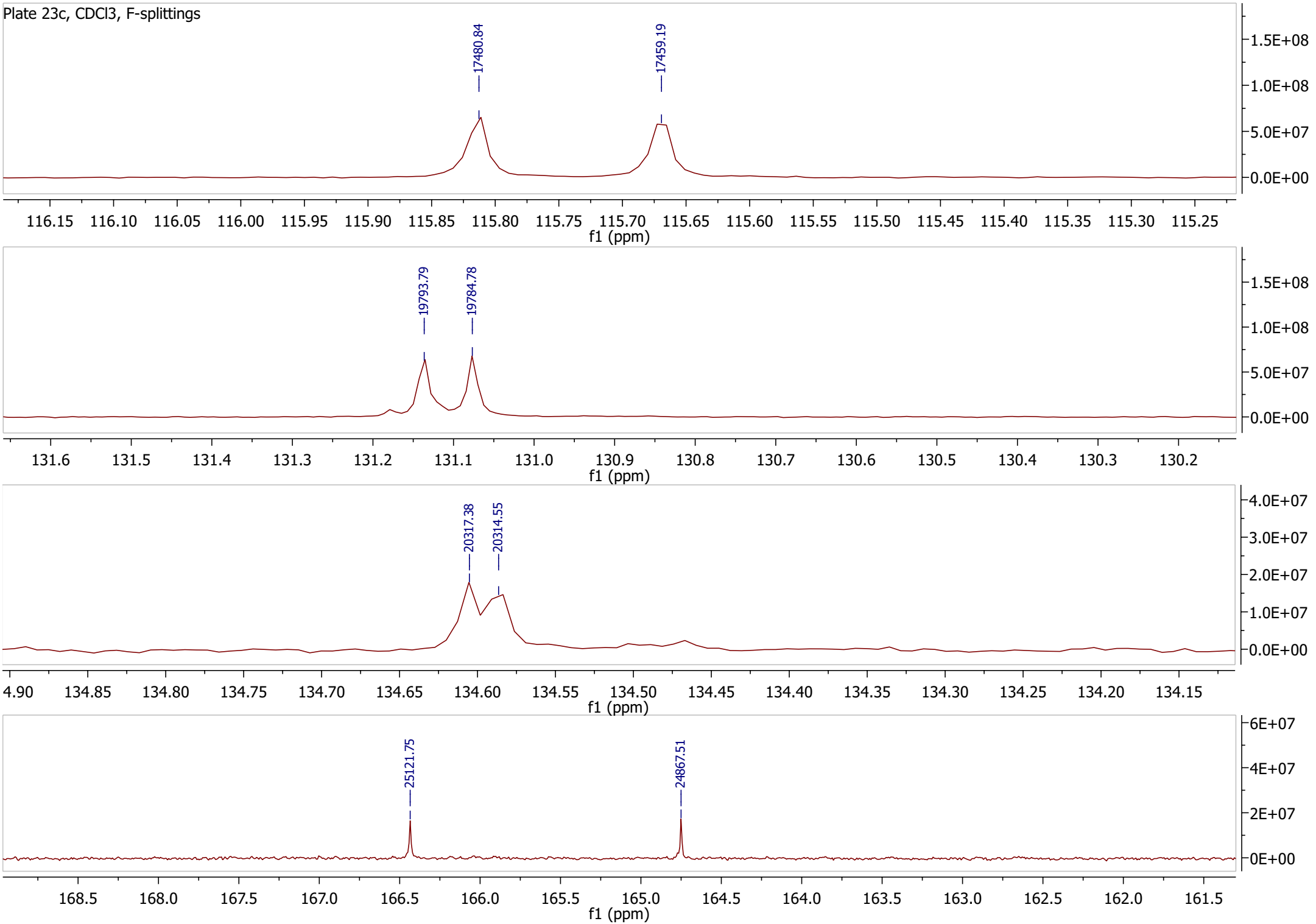


Plate 23c, CDCl3, F-splittings
17480.84
17459.19
1.5E+08
1.0E+08
5.0E+07
0.0E+00
116.15 116.10 116.05 116.00 115.95 115.90 115.85 115.80 115.75 115.70 115.65 115.60 115.55 115.50 115.45 115.40 115.35 115.30 115.25
f1 (ppm)
19793.79
19784.78
1.5E+08
1.0E+08
5.0E+07
0.0E+00
131.6 131.5 131.4 131.3 131.2 131.1 131.0 130.9 130.8 130.7 130.6 130.5 130.4 130.3 130.2
f1 (ppm)
20317.38
20314.55
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
4.90 134.85 134.80 134.75 134.70 134.65 134.60 134.55 134.50 134.45 134.40 134.35 134.30 134.25 134.20 134.15
f1 (ppm)
25121.75
24867.51
6E+07
4E+07
2E+07
0E+00
168.5 168.0 167.5 167.0 166.5 166.0 165.5 165.0 164.5 164.0 163.5 163.0 162.5 162.0 161.5
f1 (ppm)

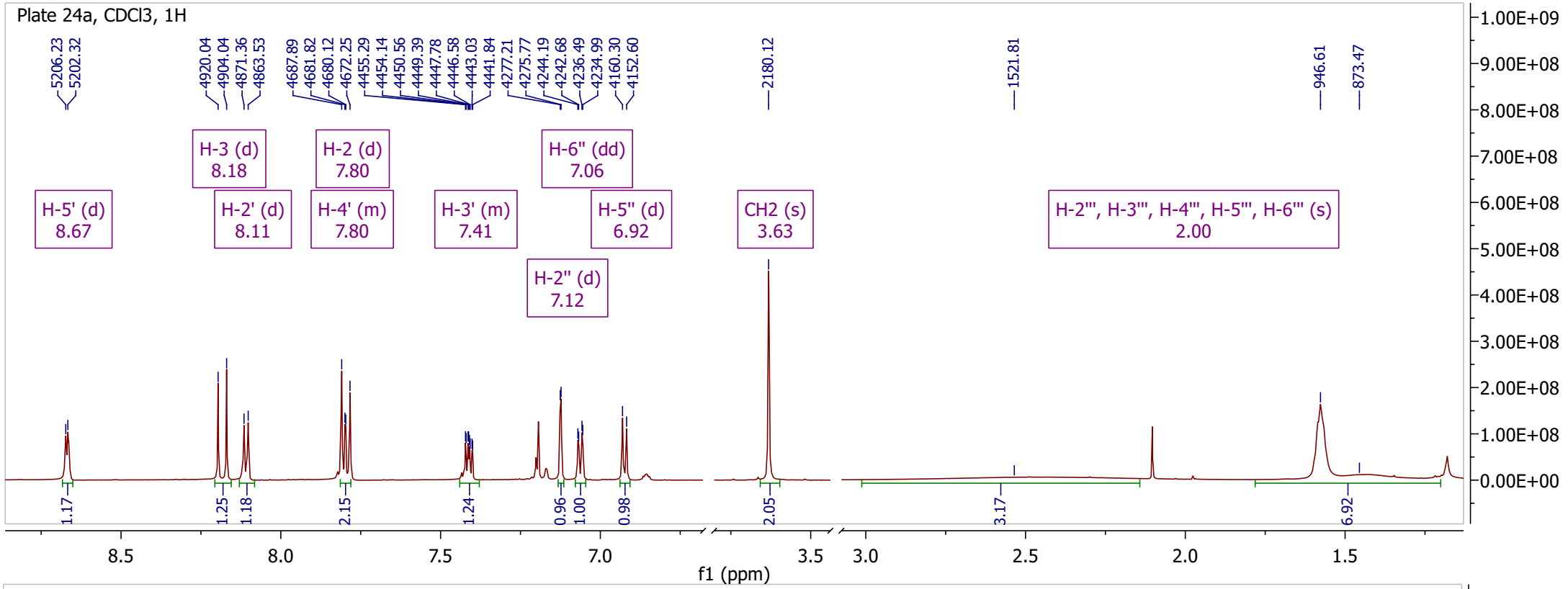
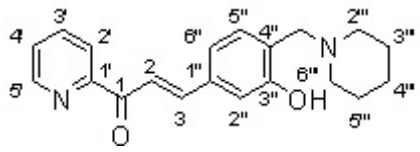


Plate 24a, CDCl3, 1H
5206.23
5202.32
4920.04
4904.04
4871.36
4863.53
4687.89
4681.82
4680.12
4672.25
4455.29
4454.14
4450.56
4449.39
4447.78
4446.58
4443.03
4441.84
4277.21
4275.77
4244.19
4242.68
4236.49
4234.99
4160.30
4152.60
2180.12
1521.81
946.61
873.47
H-3 (d) 8.18
H-2 (d) 7.80
H-6" (dd) 7.06
H-5' (d) 8.67
H-2' (d) 8.11
H-4' (m) 7.80
H-3' (m) 7.41
H-5" (d) 6.92
CH2 (s) 3.63
H-2"', H-3"', H-4"', H-5"', H-6"' (s) 2.00
H-2" (d) 7.12
1.17
1.25
1.18
2.15
1.24
0.96
1.00
0.98
2.05
3.17
6.92
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
8.5
8.0
7.5
7.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


3'
4'
2'
5'
N
1'
1
O
2
3
1"
6"
5"
4"
2"
3"
OH
N
2"'
3"'
6"'
4"'
5"'

54

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

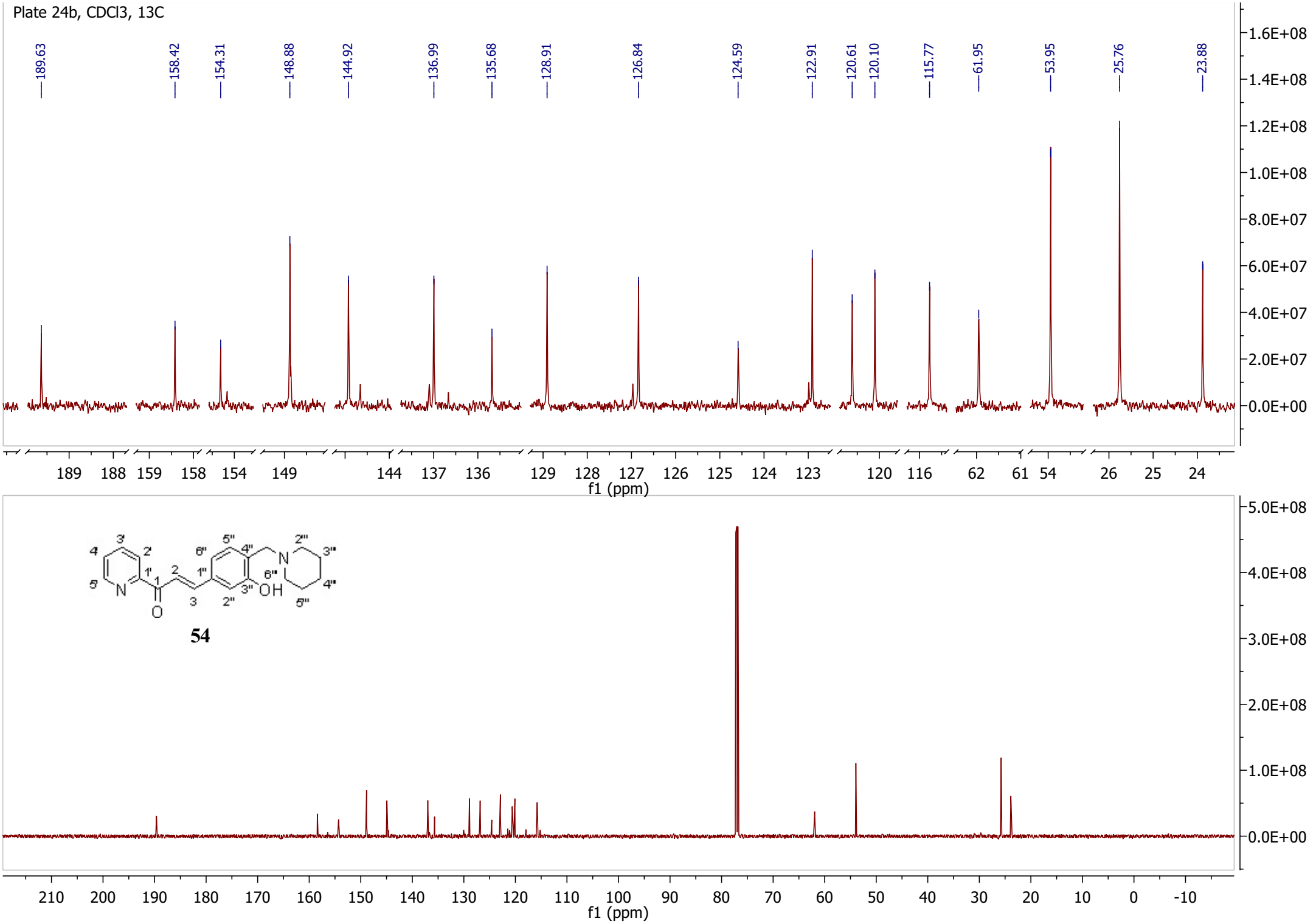


Plate 24b, CDCl3, 13C
189.63
158.42
154.31
148.88
144.92
136.99
135.68
128.91
126.84
124.59
122.91
120.61
120.10
115.77
61.95
53.95
25.76
23.88
1.6E+08
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
189 188 159 158 154 149 144 137 136 129 128 127 126 125 124 123 120 116 62 61 54 26 25 24
f1 (ppm)
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

54

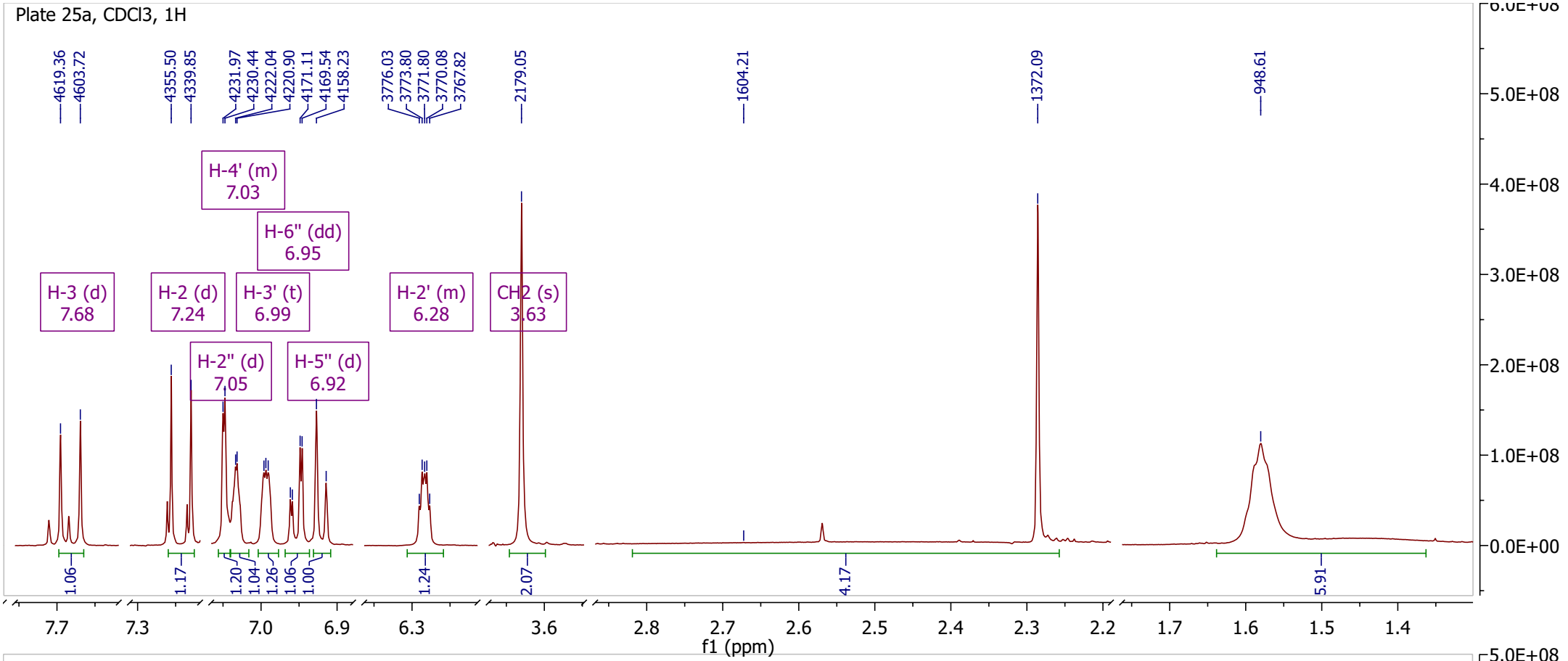
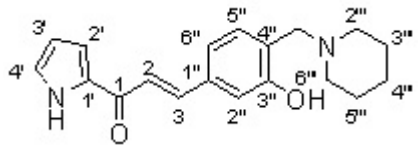


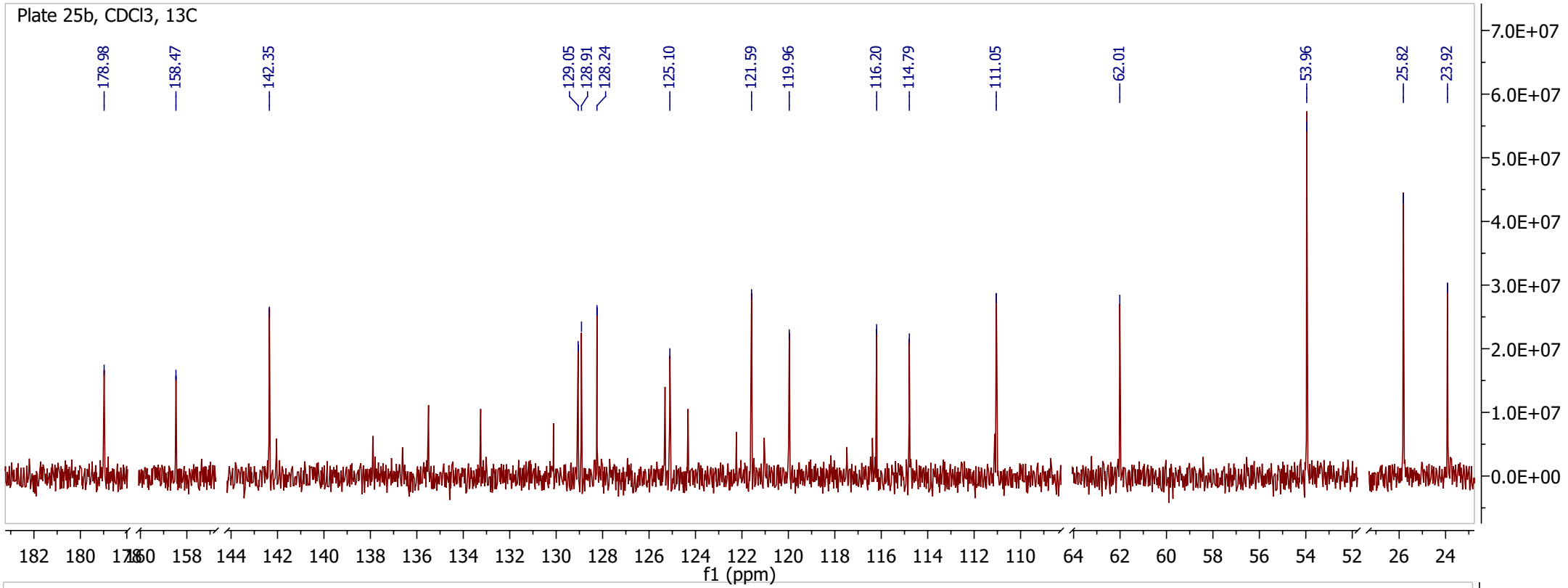
Plate 25a, CDCl3, 1H
4619.36
4603.72
4355.50
4339.85
4231.97
4230.44
4222.04
4220.90
4171.11
4169.54
4158.23
3776.03
3773.80
3771.80
3770.08
3767.82
2179.05
1604.21
1372.09
948.61
H-4' (m) 7.03
H-6" (dd) 6.95
H-3 (d) 7.68
H-2 (d) 7.24
H-3' (t) 6.99
H-2' (m) 6.28
CH2 (s) 3.63
H-2" (d) 7.05
H-5" (d) 6.92
1.06
1.17
1.20
1.04
1.26
1.06
1.00
1.24
2.07
4.17
5.91
f1 (ppm)

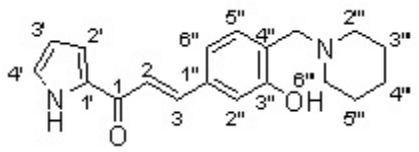


55

f1 (ppm)

Plate 25b, CDCl3, 13C





55

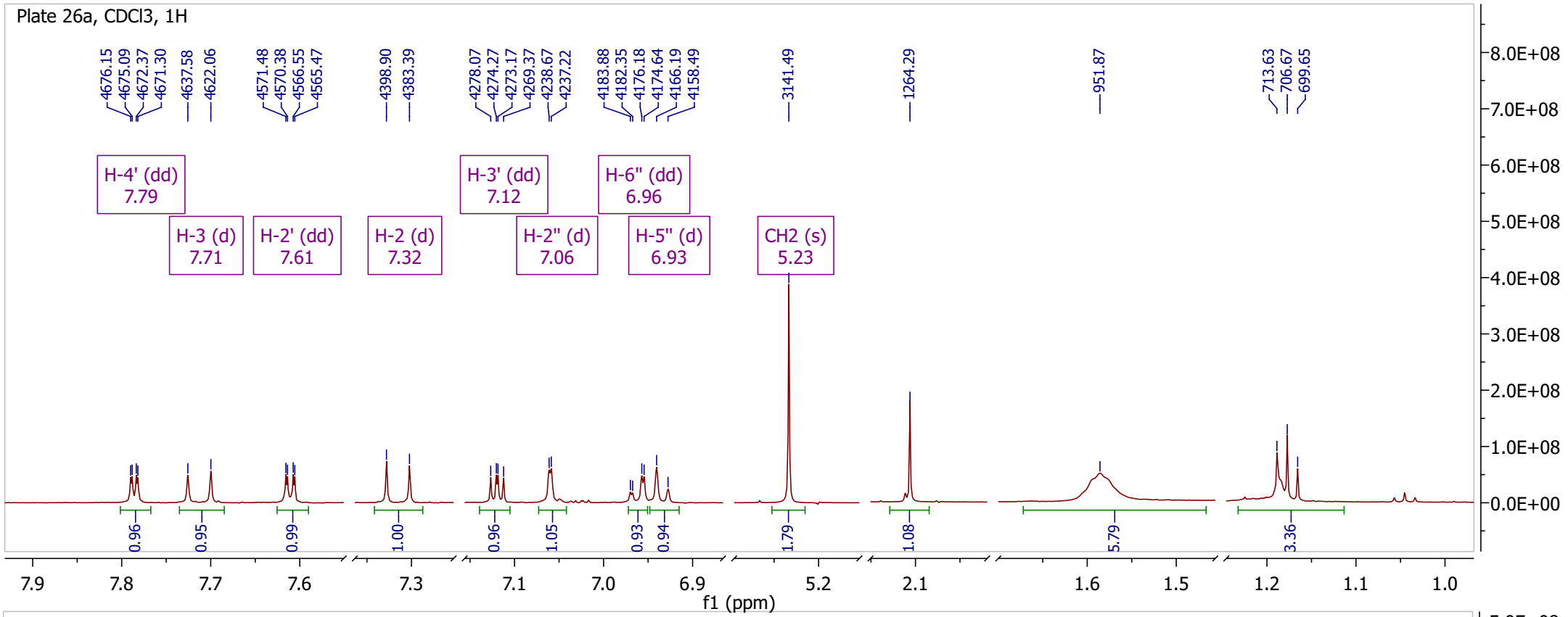
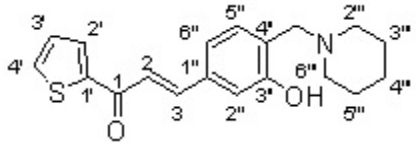


Plate 26a, CDCl3, 1H
4676.15
4675.09
4672.37
4671.30
4637.58
4622.06
4571.48
4570.38
4566.55
4565.47
4398.90
4383.39
4278.07
4274.27
4273.17
4269.37
4238.67
4237.22
4183.88
4182.35
4176.18
4174.64
4166.19
4158.49
3141.49
1264.29
951.87
713.63
706.67
699.65
H-4' (dd) 7.79
H-3 (d) 7.71
H-2' (dd) 7.61
H-2 (d) 7.32
H-3' (dd) 7.12
H-2" (d) 7.06
H-6" (dd) 6.96
H-5" (d) 6.93
CH2 (s) 5.23
0.96
0.95
0.99
1.00
0.96
1.05
0.93
0.94
1.79
1.08
5.79
3.36
f1 (ppm)



56

f1 (ppm)

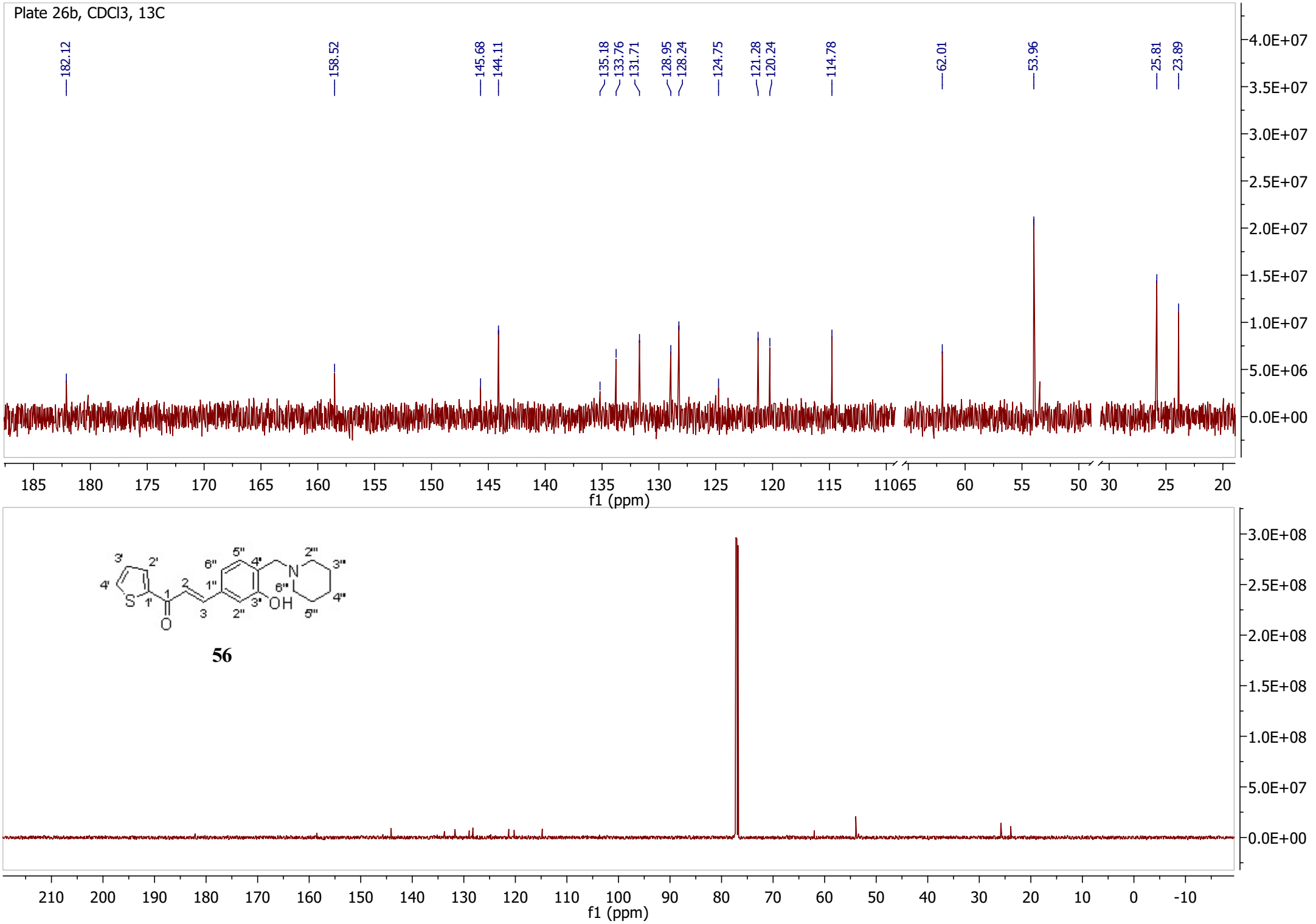


Plate 26b, CDCl3, 13C
182.12
158.52
145.68
144.11
135.18
133.76
131.71
128.95
128.24
124.75
121.28
120.24
114.78
62.01
53.96
25.81
23.89
f1 (ppm)
f1 (ppm)

3'
2'
4'
S
1'
1
2
3
O
1"
6"
5"
4"
3"
2"
N
2"
3"
6"
4"
OH
5"

56

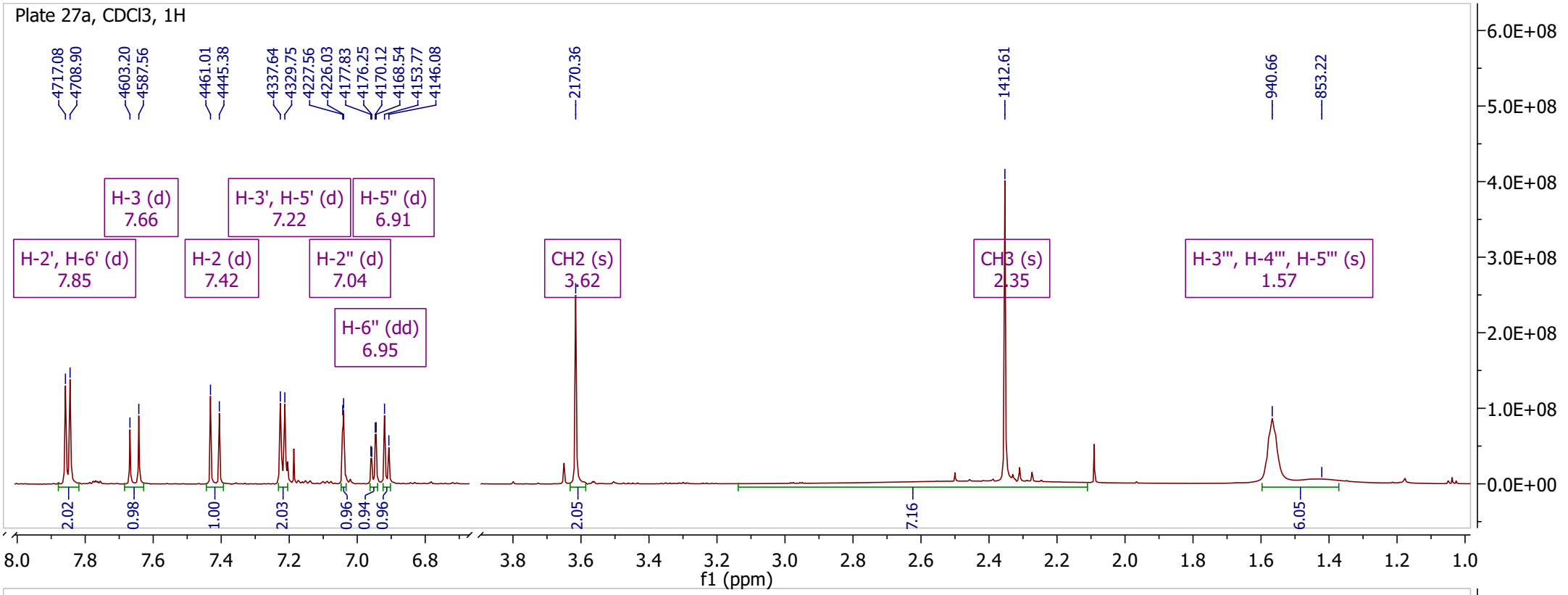
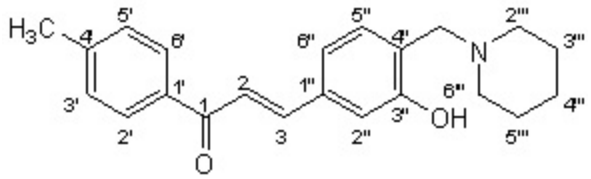


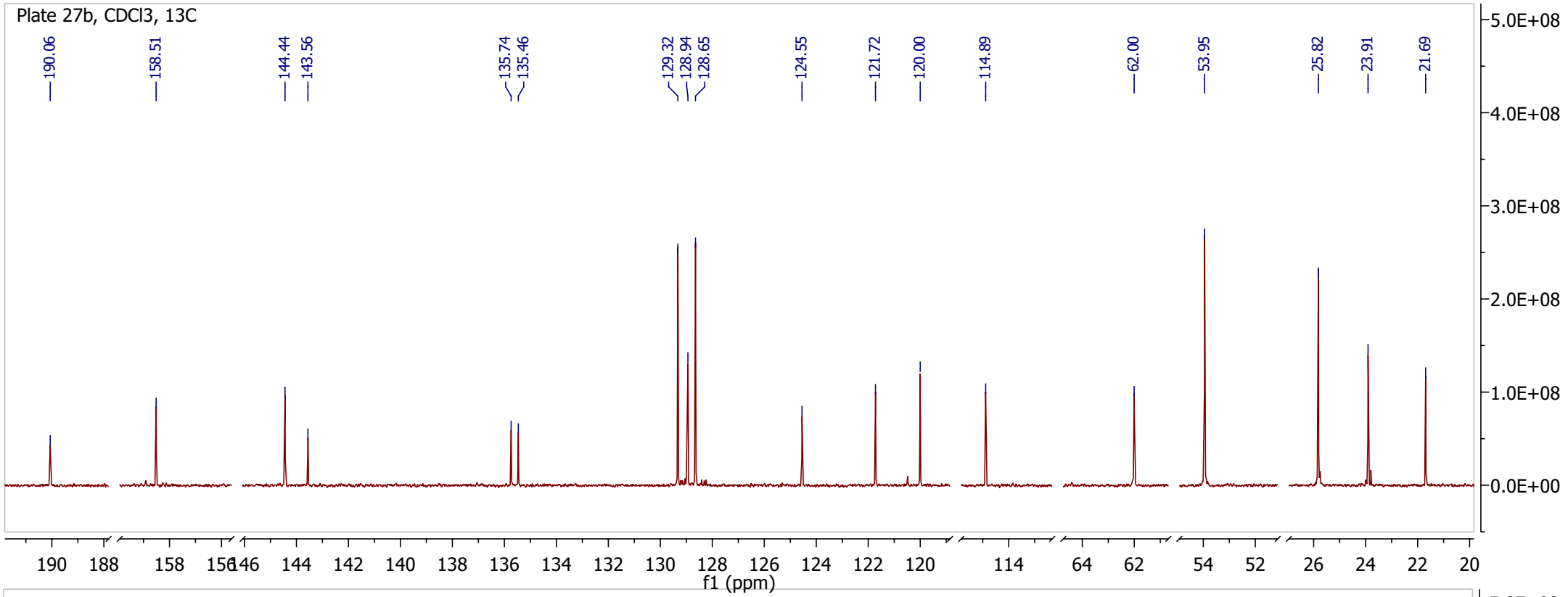
Plate 27a, CDCl3, 1H
4717.08
4708.90
4603.20
4587.56
4461.01
4445.38
4337.64
4329.75
4227.56
4226.03
4177.83
4176.25
4170.12
4168.54
4153.77
4146.08
2170.36
1412.61
940.66
853.22
H-3 (d) 7.66
H-3', H-5' (d) 7.22
H-5" (d) 6.91
H-2', H-6' (d) 7.85
H-2 (d) 7.42
H-2" (d) 7.04
CH2 (s) 3.62
CH3 (s) 2.35
H-3"', H-4"', H-5"' (s) 1.57
H-6" (dd) 6.95
2.02
0.98
1.00
2.03
0.96
0.94
0.96
2.05
7.16
6.05
f1 (ppm)

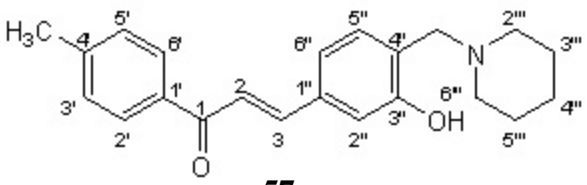

H3C
OH
N
O

57

f1 (ppm)

Plate 27b, CDCl3, 13C





57

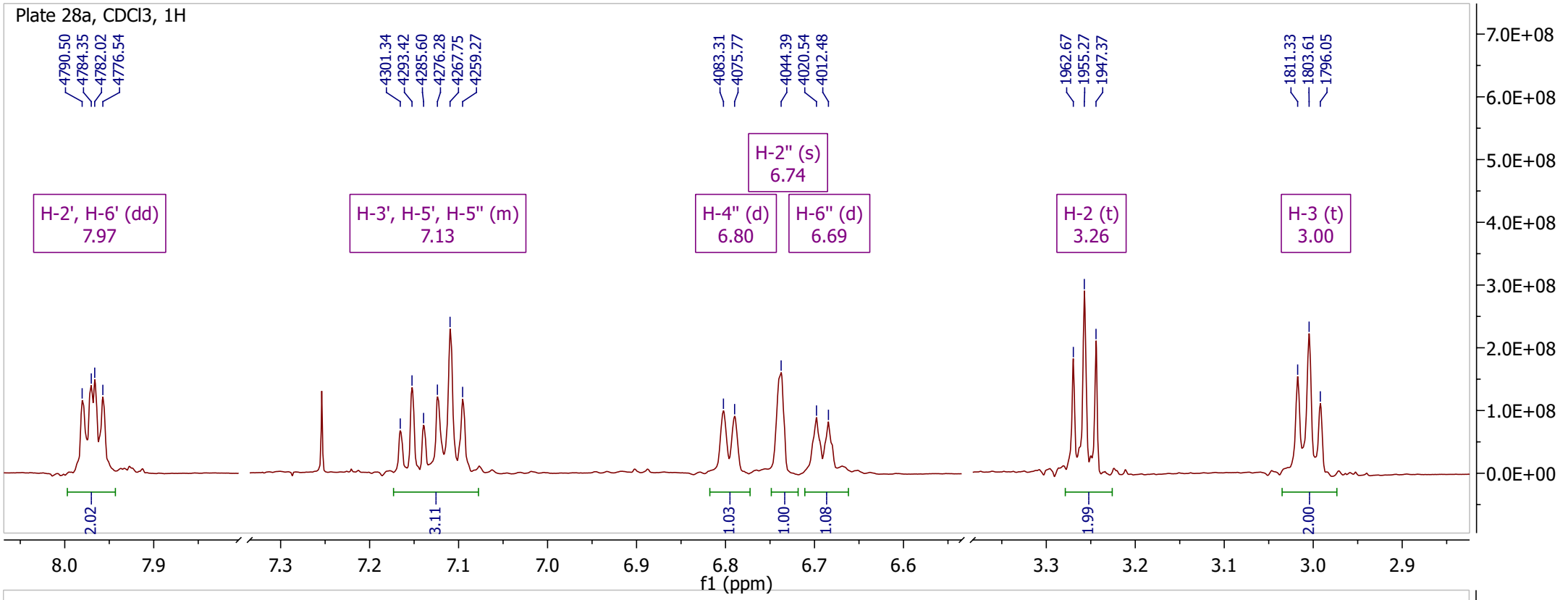
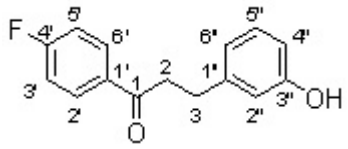


Plate 28a, CDCl3, 1H
4790.50
4784.35
4782.02
4776.54
4301.34
4293.42
4285.60
4276.28
4267.75
4259.27
4083.31
4075.77
4044.39
4020.54
4012.48
1962.67
1955.27
1947.37
1811.33
1803.61
1796.05
H-2" (s)
6.74
H-2', H-6' (dd)
7.97
H-3', H-5', H-5" (m)
7.13
H-4" (d)
6.80
H-6" (d)
6.69
H-2 (t)
3.26
H-3 (t)
3.00
2.02
3.11
1.03
1.00
1.08
1.99
2.00
f1 (ppm)


F
OH
O

109

f1 (ppm)

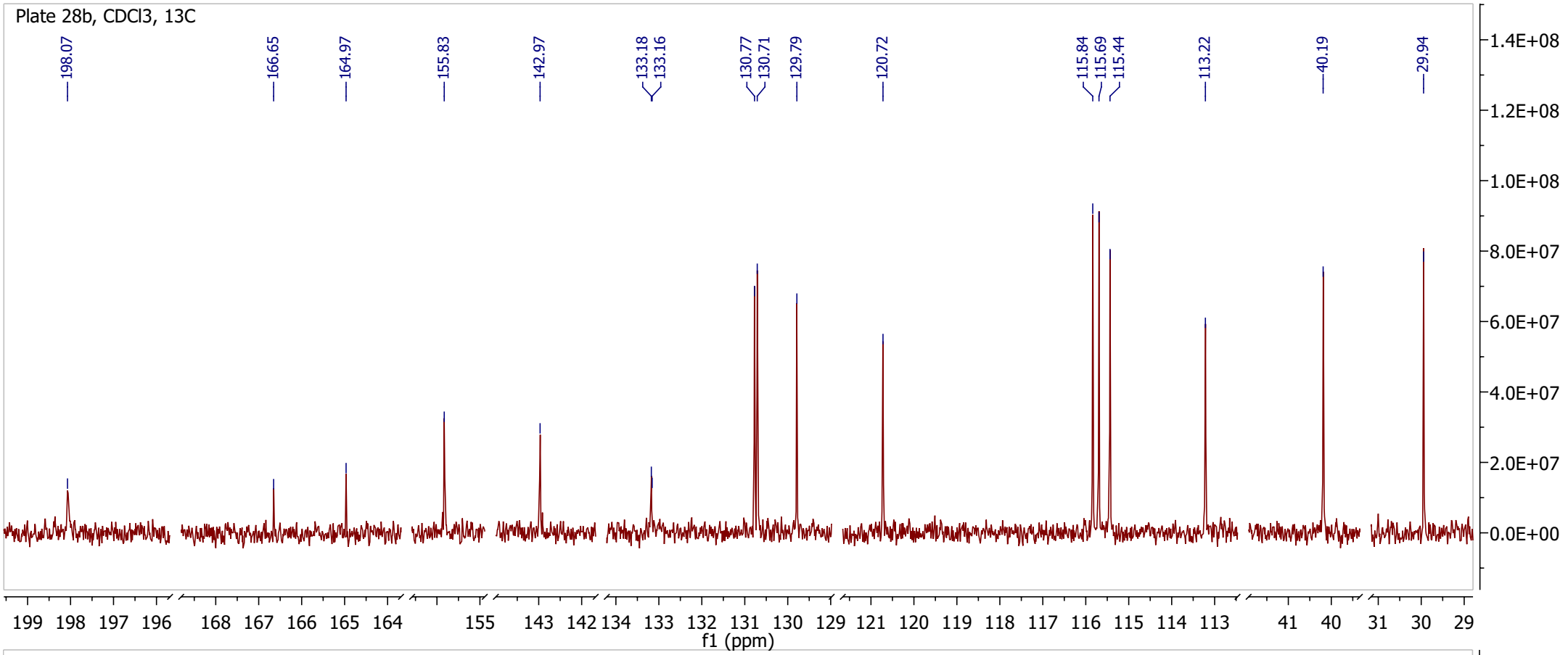
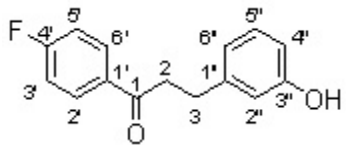


Plate 28b, CDCl3, 13C
198.07
166.65
164.97
155.83
142.97
133.18
133.16
130.77
130.71
129.79
120.72
115.84
115.69
115.44
113.22
40.19
29.94
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
199 198 197 196 168 167 166 165 164 155 143 142 134 133 132 131 130 129 121 120 119 118 117 116 115 114 113 41 40 31 30 29
f1 (ppm)


F
OH
O

109

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

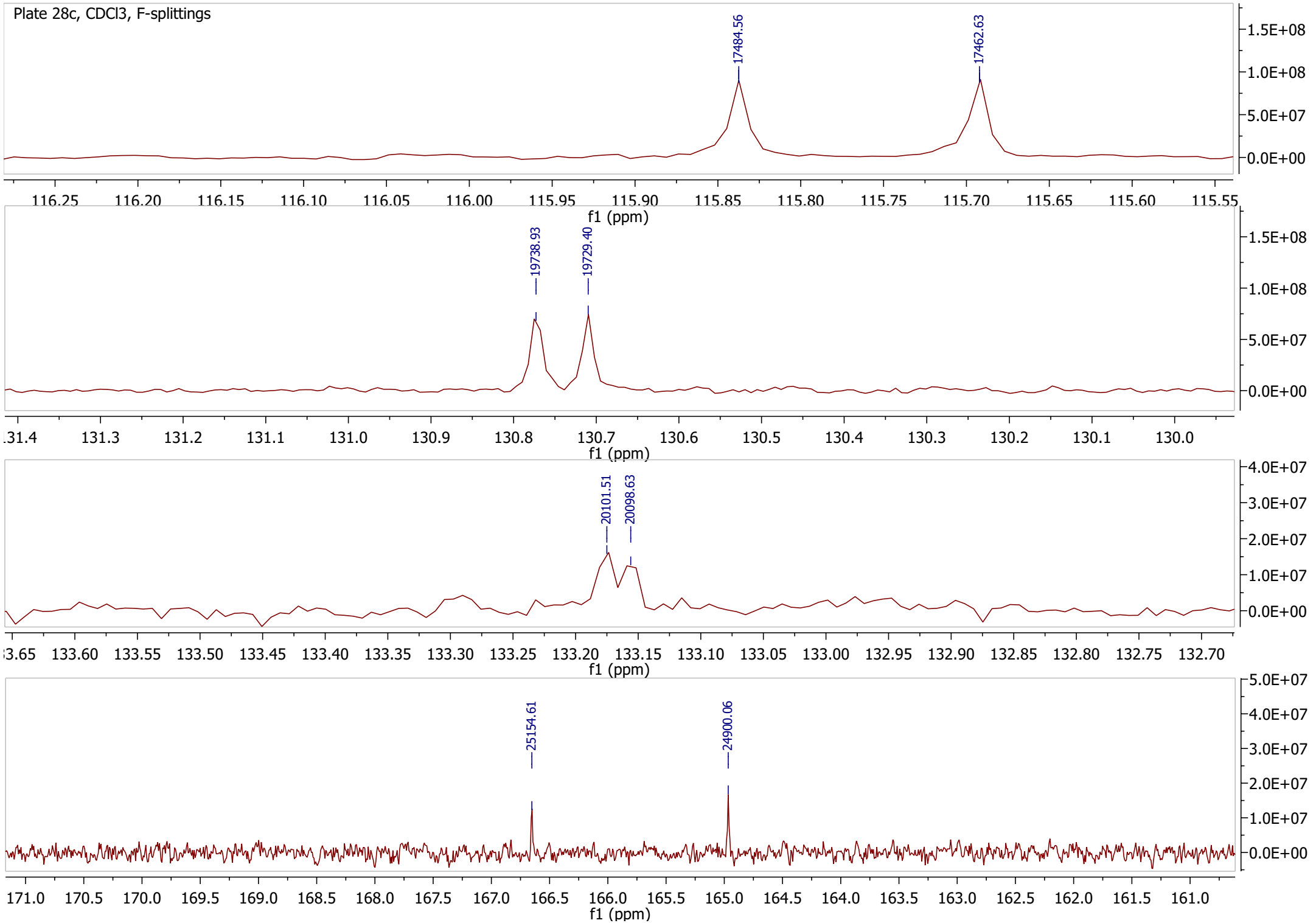


Plate 28c, CDCl3, F-splittings
17484.56
17462.63
1.5E+08
1.0E+08
5.0E+07
0.0E+00
116.25 116.20 116.15 116.10 116.05 116.00 115.95 115.90 115.85 115.80 115.75 115.70 115.65 115.60 115.55
f1 (ppm)
19738.93
19729.40
1.5E+08
1.0E+08
5.0E+07
0.0E+00
131.4 131.3 131.2 131.1 131.0 130.9 130.8 130.7 130.6 130.5 130.4 130.3 130.2 130.1 130.0
f1 (ppm)
20101.51
20098.63
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
133.65 133.60 133.55 133.50 133.45 133.40 133.35 133.30 133.25 133.20 133.15 133.10 133.05 133.00 132.95 132.90 132.85 132.80 132.75 132.70
f1 (ppm)
25154.61
24900.06
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
171.0 170.5 170.0 169.5 169.0 168.5 168.0 167.5 167.0 166.5 166.0 165.5 165.0 164.5 164.0 163.5 163.0 162.5 162.0 161.5 161.0
f1 (ppm)

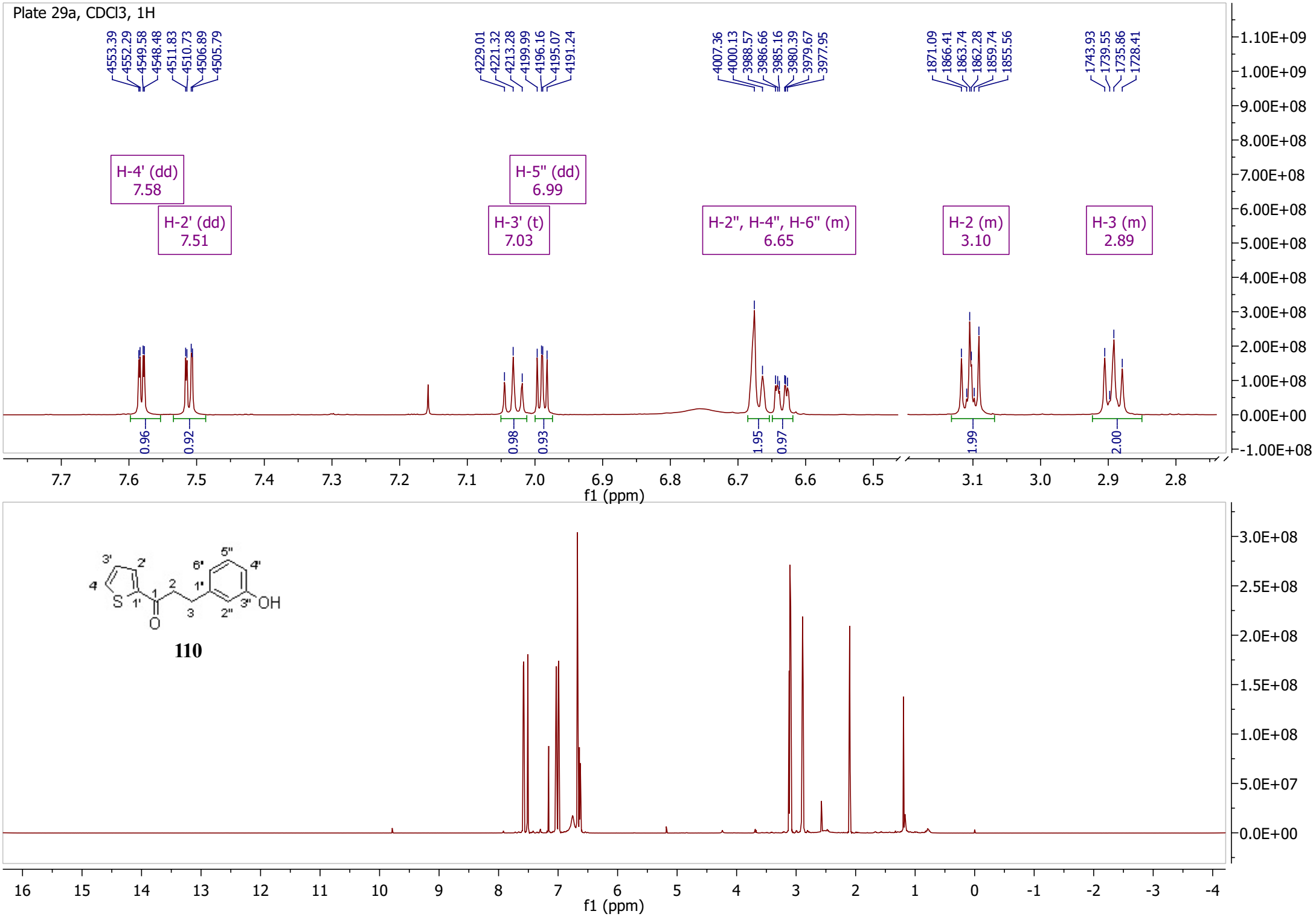


Plate 29a, CDCl3, 1H
4553.39
4552.29
4549.58
4548.48
4511.83
4510.73
4506.89
4505.79
4229.01
4221.32
4213.28
4199.99
4196.16
4195.07
4191.24
4007.36
4000.13
3988.57
3986.66
3985.16
3980.39
3979.67
3977.95
1871.09
1866.41
1863.74
1862.28
1859.74
1855.56
1743.93
1739.55
1735.86
1728.41
H-4' (dd)
7.58
H-2' (dd)
7.51
H-5" (dd)
6.99
H-3' (t)
7.03
H-2", H-4", H-6" (m)
6.65
H-2 (m)
3.10
H-3 (m)
2.89
0.96
0.92
0.98
0.93
1.95
0.97
1.99
2.00
f1 (ppm)
110
f1 (ppm)

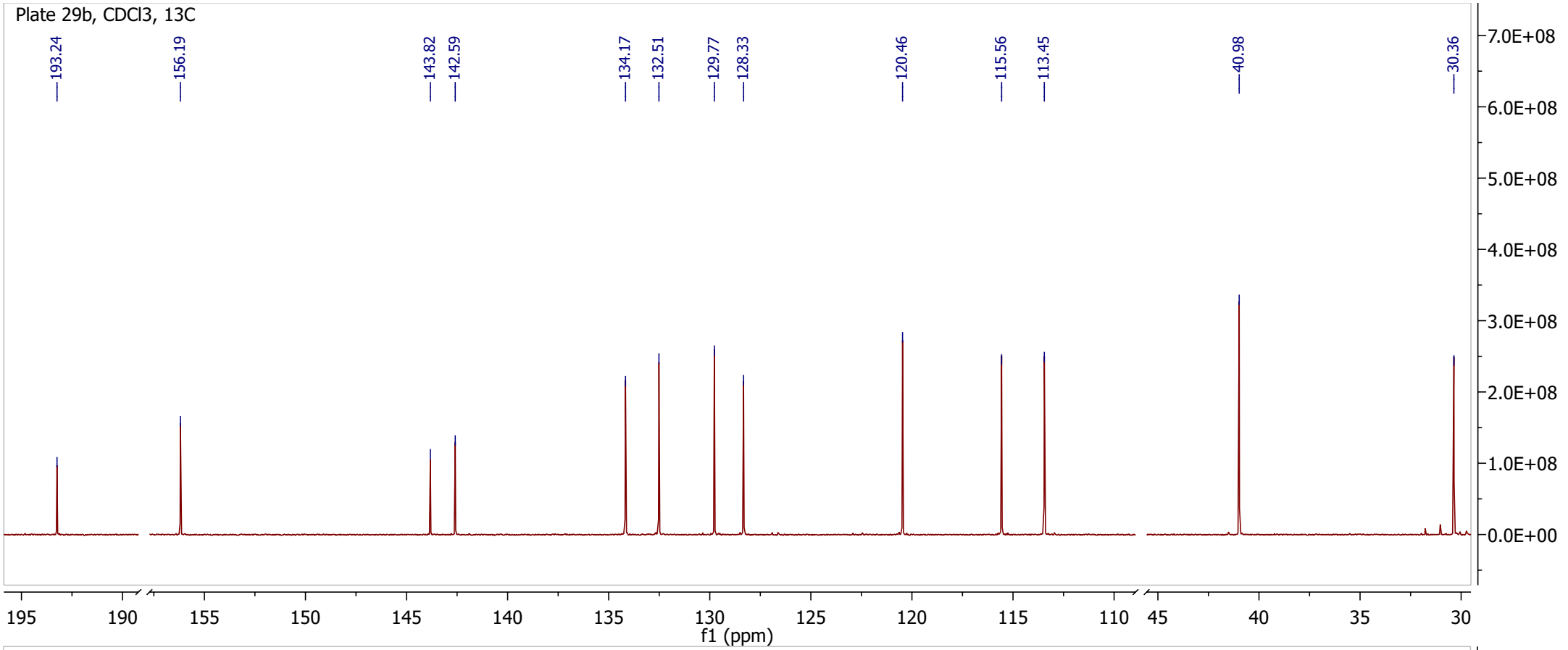
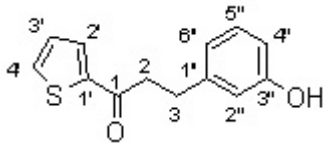


Plate 29b, CDCl3, 13C
193.24
156.19
143.82
142.59
134.17
132.51
129.77
128.33
120.46
115.56
113.45
40.98
30.36
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
195 190 155 150 145 140 135 130 125 120 115 110 45 40 35 30
f1 (ppm)


3'
2'
4'
5"
6"
4
S
1'
1
2
1"
3
2"
3"
OH
O

110

3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

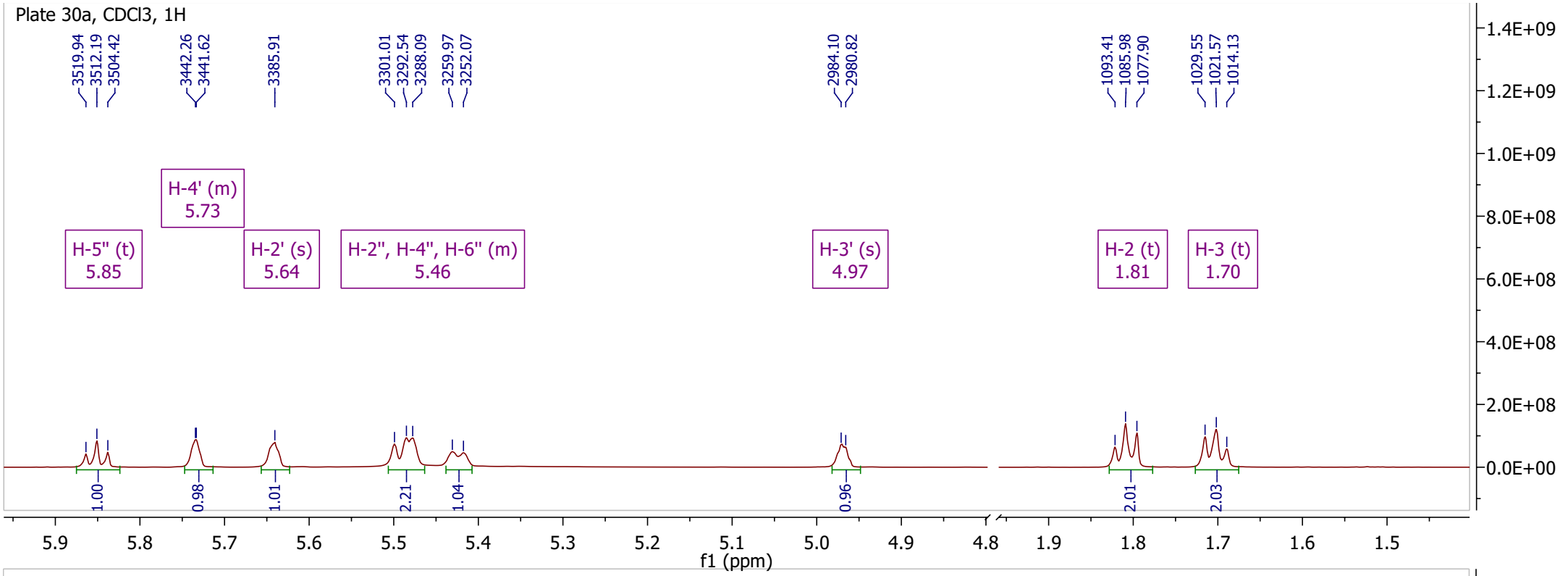
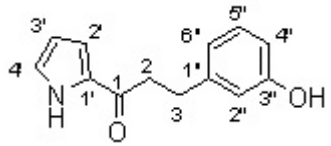


Plate 30a, CDCl3, 1H
3519.94
3512.19
3504.42
3442.26
3441.62
3385.91
3301.01
3292.54
3288.09
3259.97
3252.07
2984.10
2980.82
1093.41
1085.98
1077.90
1029.55
1021.57
1014.13
H-4' (m)
5.73
H-5" (t)
5.85
H-2' (s)
5.64
H-2", H-4", H-6" (m)
5.46
H-3' (s)
4.97
H-2 (t)
1.81
H-3 (t)
1.70
1.00
0.98
1.01
2.21
1.04
0.96
2.01
2.03
f1 (ppm)


3'
2'
4'
5'
6'
1'
2
1
3
2"
3"
OH
N
H
O

111

f1 (ppm)

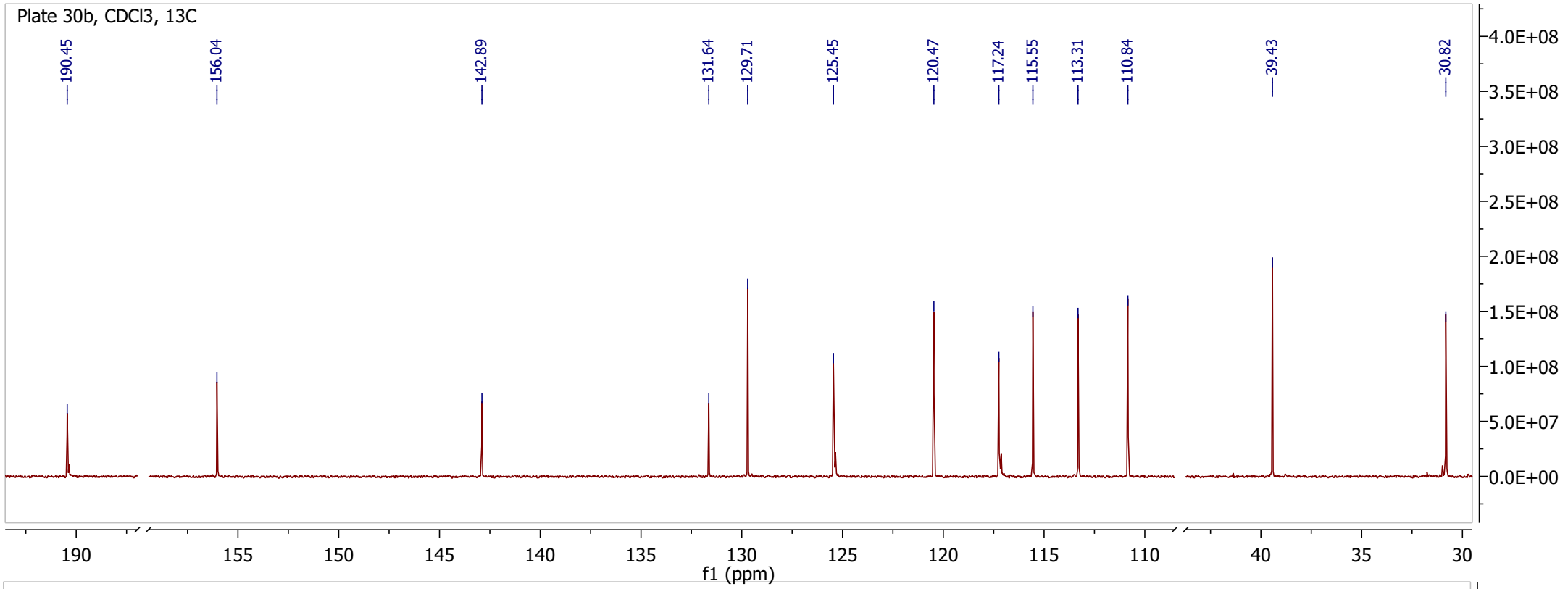
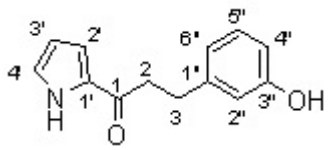


Plate 30b, CDCl3, 13C
190.45
156.04
142.89
131.64
129.71
125.45
120.47
117.24
115.55
113.31
110.84
39.43
30.82
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
190
155
150
145
140
135
130
125
120
115
110
40
35
30
f1 (ppm)


3'
2'
4'
5'
6'
1'
2
4
N
H
1'
1
2
3
O
2'
3'
OH

111

2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

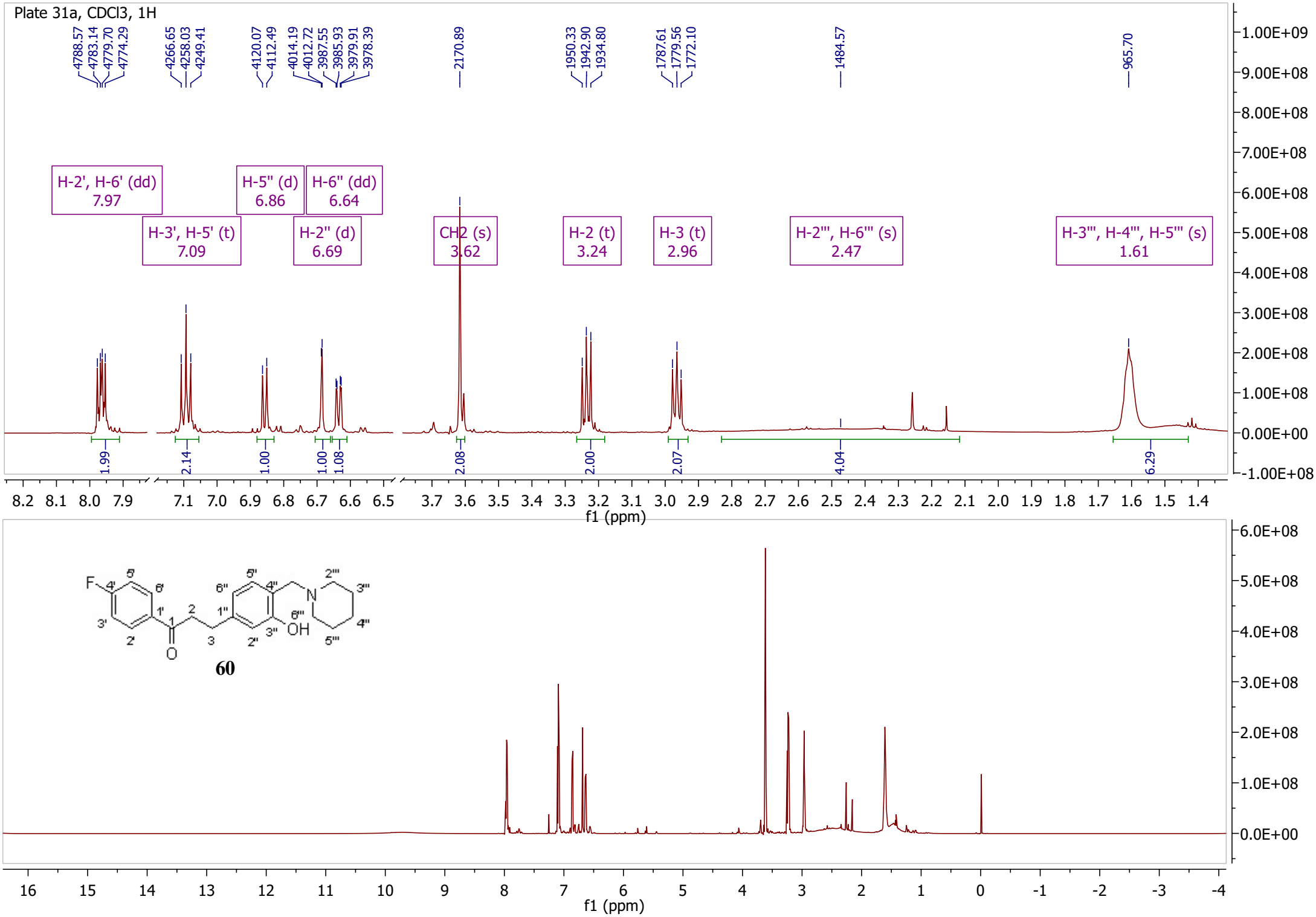


Plate 31a, CDCl3, 1H
4788.57
4783.14
4779.70
4774.29
4266.65
4258.03
4249.41
4120.07
4112.49
4014.19
4012.72
3987.55
3985.93
3979.91
3978.39
2170.89
1950.33
1942.90
1934.80
1787.61
1779.56
1772.10
1484.57
965.70
H-2', H-6' (dd) 7.97
H-3', H-5' (t) 7.09
H-5" (d) 6.86
H-6" (dd) 6.64
H-2" (d) 6.69
CH2 (s) 3.62
H-2 (t) 3.24
H-3 (t) 2.96
H-2"', H-6"' (s) 2.47
H-3"', H-4"', H-5"' (s) 1.61
1.99
2.14
1.00
1.00
1.08
2.08
2.00
2.07
4.04
6.29
f1 (ppm)
F
O
OH
N
60
f1 (ppm)

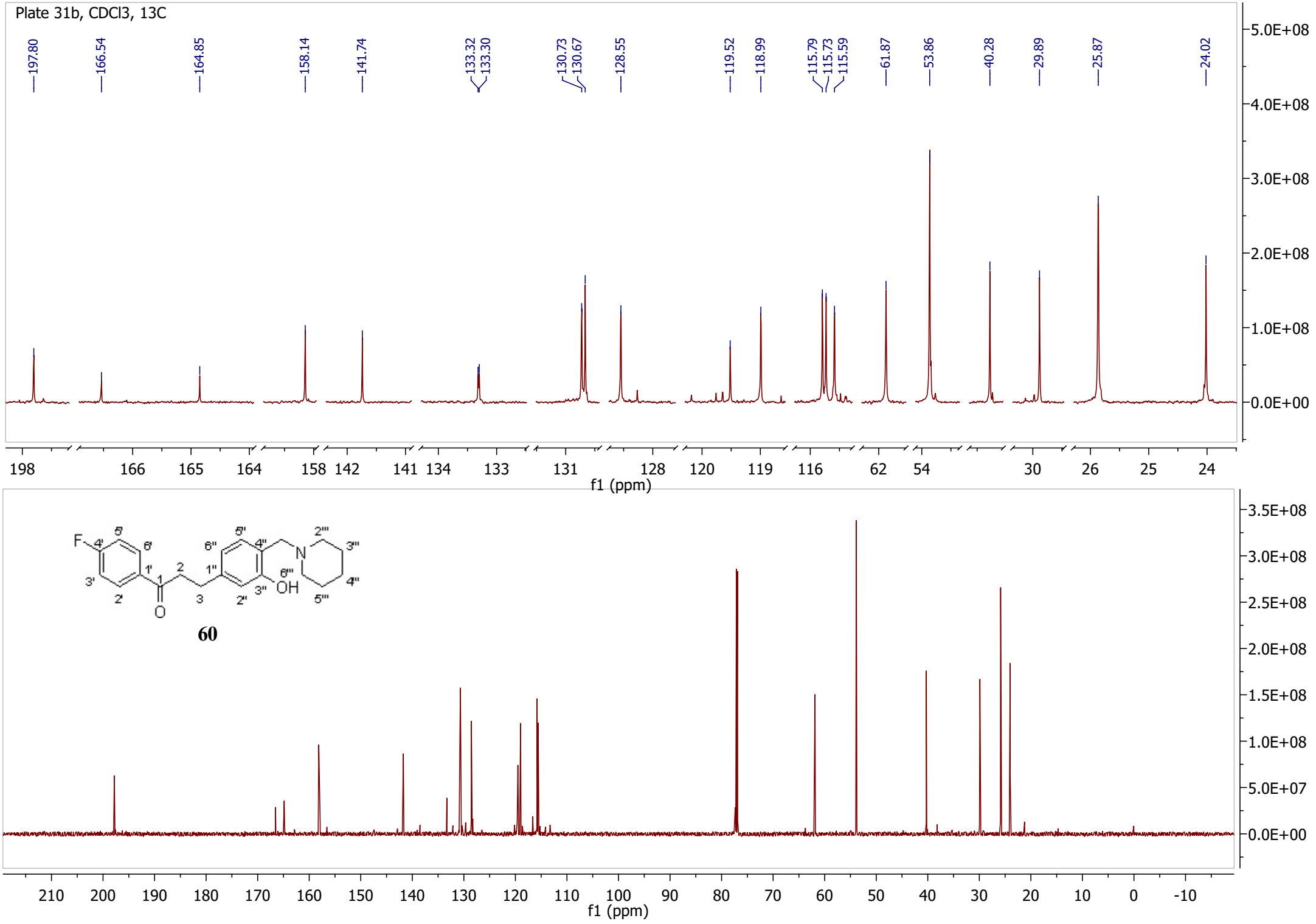


Plate 31b, CDCl3, 13C
197.80
166.54
164.85
158.14
141.74
133.32
133.30
130.73
130.67
128.55
119.52
118.99
115.79
115.73
115.59
61.87
53.86
40.28
29.89
25.87
24.02
f1 (ppm)
f1 (ppm)
60

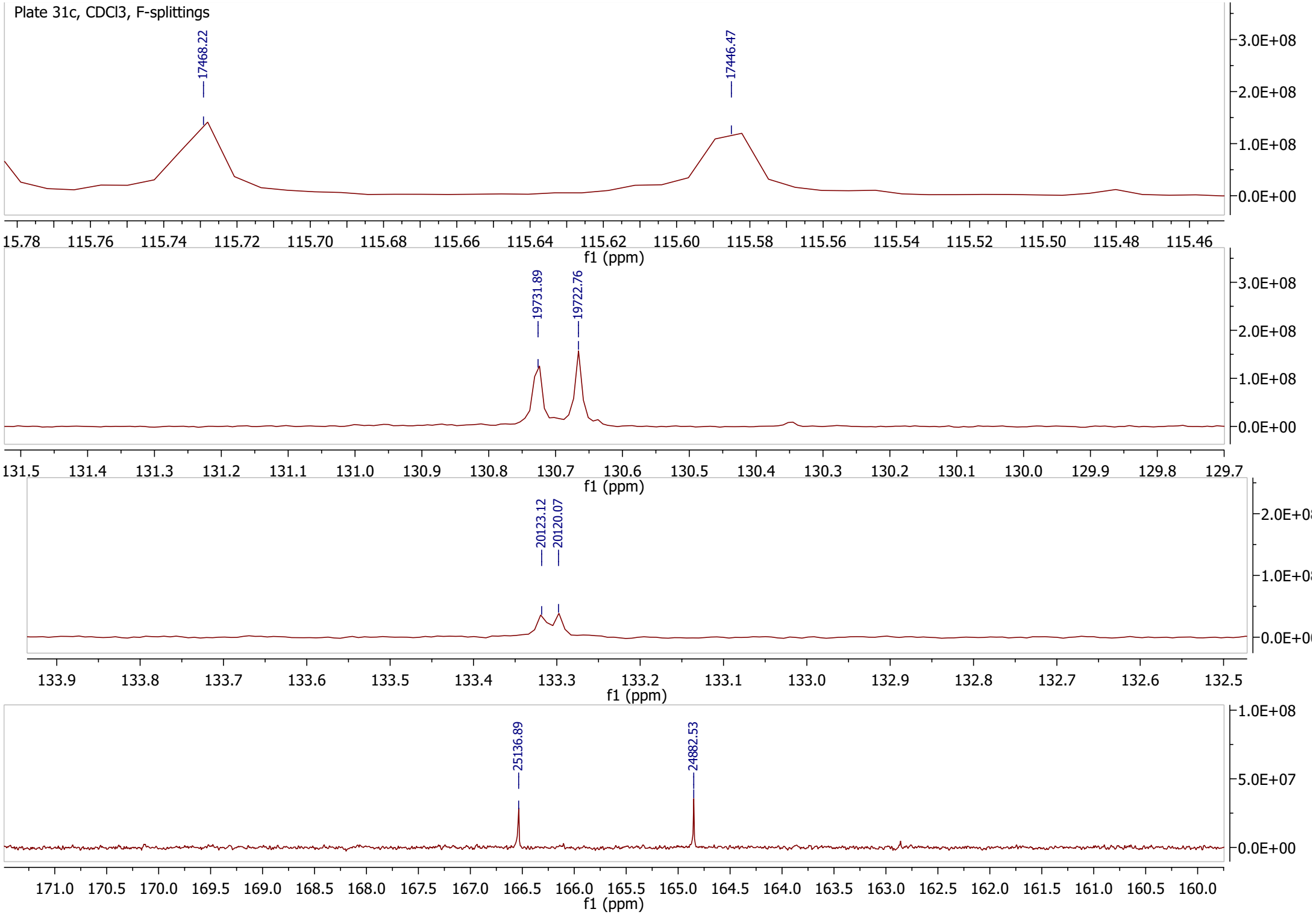


Plate 31c, CDCl3, F-splittings
17468.22
17446.47
3.0E+08
2.0E+08
1.0E+08
0.0E+00
15.78 115.76 115.74 115.72 115.70 115.68 115.66 115.64 115.62 115.60 115.58 115.56 115.54 115.52 115.50 115.48 115.46
f1 (ppm)
19731.89
19722.76
3.0E+08
2.0E+08
1.0E+08
0.0E+00
131.5 131.4 131.3 131.2 131.1 131.0 130.9 130.8 130.7 130.6 130.5 130.4 130.3 130.2 130.1 130.0 129.9 129.8 129.7
f1 (ppm)
20123.12
20120.07
2.0E+0
1.0E+0
0.0E+0
133.9 133.8 133.7 133.6 133.5 133.4 133.3 133.2 133.1 133.0 132.9 132.8 132.7 132.6 132.5
f1 (ppm)
25136.89
24882.53
1.0E+08
5.0E+07
0.0E+00
171.0 170.5 170.0 169.5 169.0 168.5 168.0 167.5 167.0 166.5 166.0 165.5 165.0 164.5 164.0 163.5 163.0 162.5 162.0 161.5 161.0 160.5 160.0
f1 (ppm)

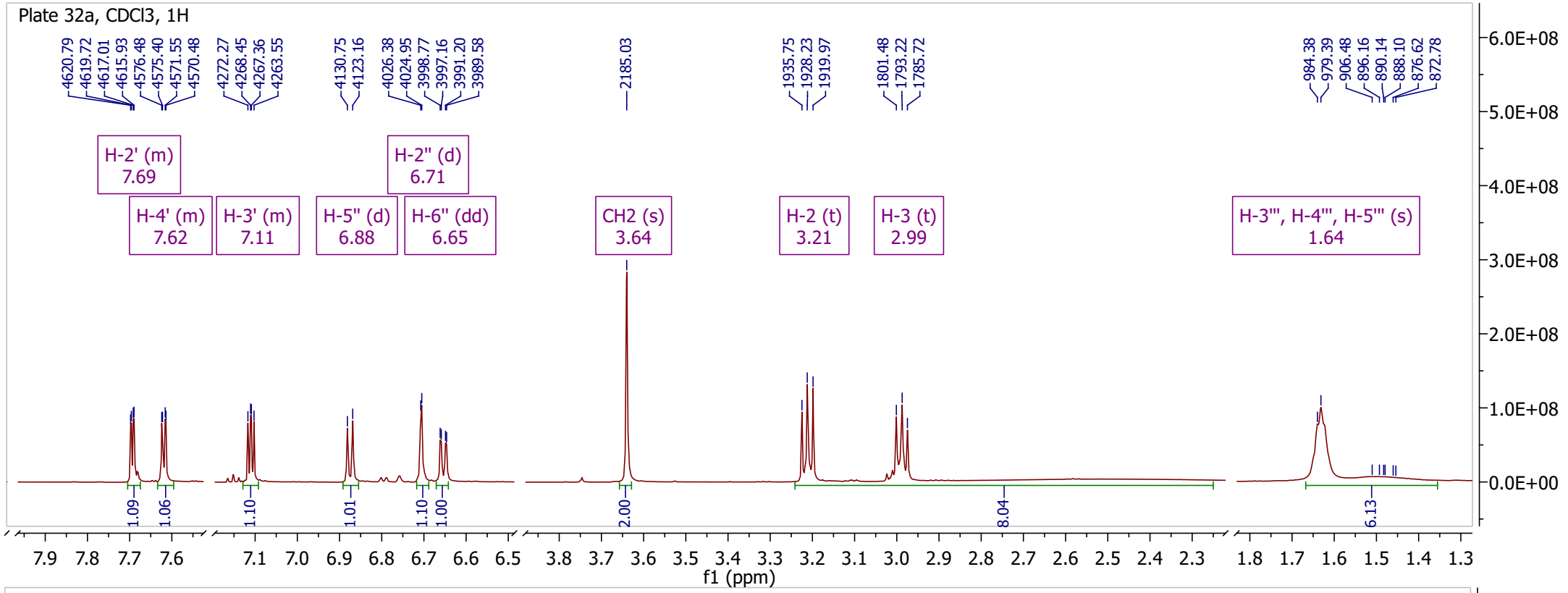
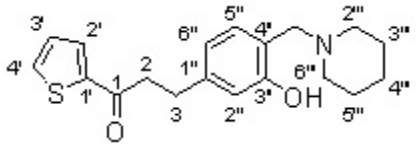


Plate 32a, CDCl3, 1H
4620.79
4619.72
4617.01
4615.93
4576.48
4575.40
4571.55
4570.48
4272.27
4268.45
4267.36
4263.55
4130.75
4123.16
4026.38
4024.95
3998.77
3997.16
3991.20
3989.58
2185.03
1935.75
1928.23
1919.97
1801.48
1793.22
1785.72
984.38
979.39
906.48
896.16
890.14
888.10
876.62
872.78
H-2' (m)
7.69
H-4' (m)
7.62
H-3' (m)
7.11
H-5" (d)
6.88
H-2" (d)
6.71
H-6" (dd)
6.65
CH2 (s)
3.64
H-2 (t)
3.21
H-3 (t)
2.99
H-3'", H-4'", H-5'" (s)
1.64
1.09
1.06
1.10
1.01
1.10
1.00
2.00
8.04
6.13
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.9 7.8 7.7 7.6 7.1 7.0 6.9 6.8 6.7 6.6 6.5 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)


3'
2'
4'
S
1'
1
2
3
O
6"
5"
4'
1"
2"
3'
OH
2'''
3'''
N
6'''
4'''
5'''

61

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

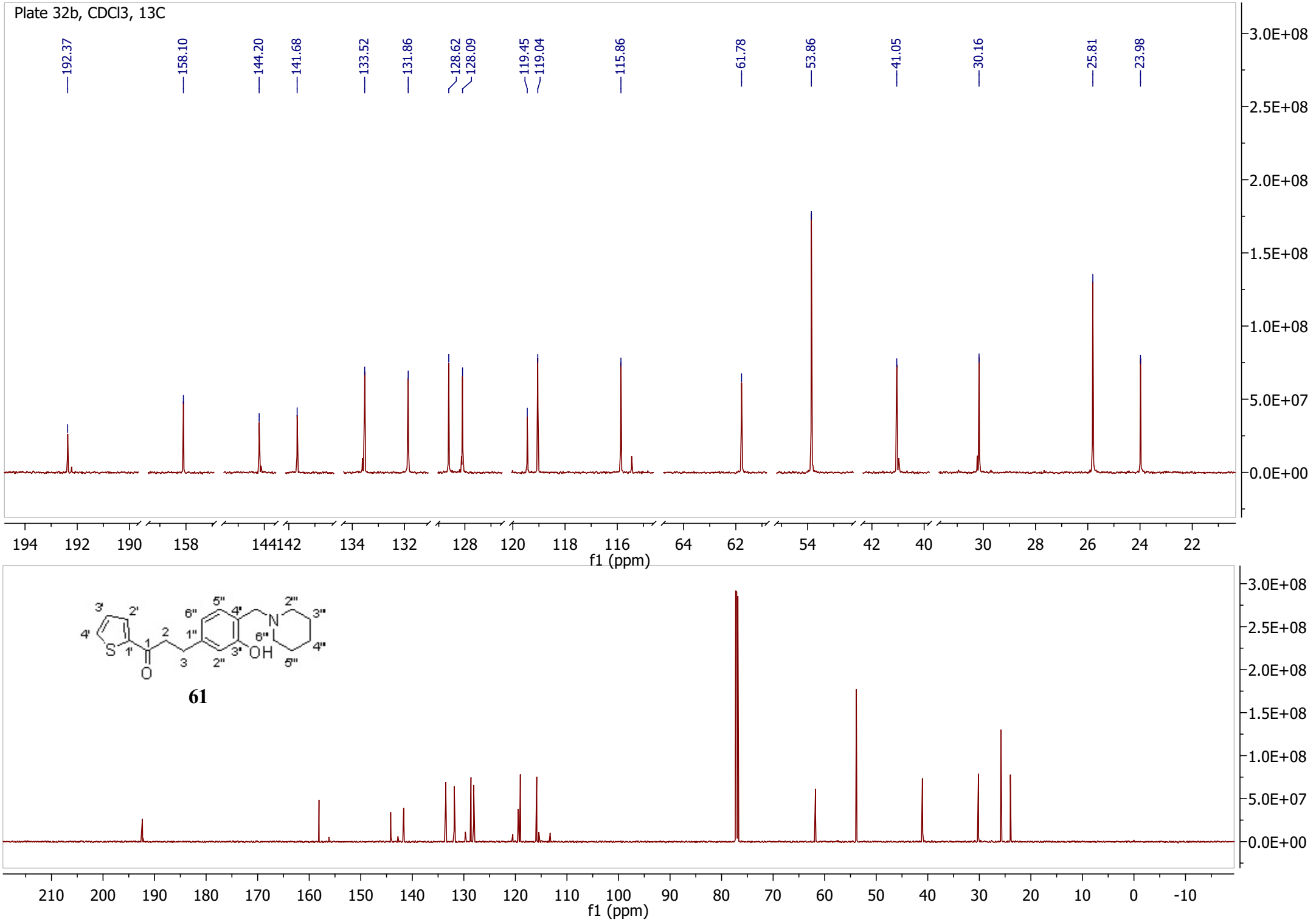


Plate 32b, CDCl3, 13C
192.37
158.10
144.20
141.68
133.52
131.86
128.62
128.09
119.45
119.04
115.86
61.78
53.86
41.05
30.16
25.81
23.98
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
194 192 190 158 144 142 134 132 128 120 118 116 64 62 54 42 40 30 28 26 24 22
f1 (ppm)
61
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

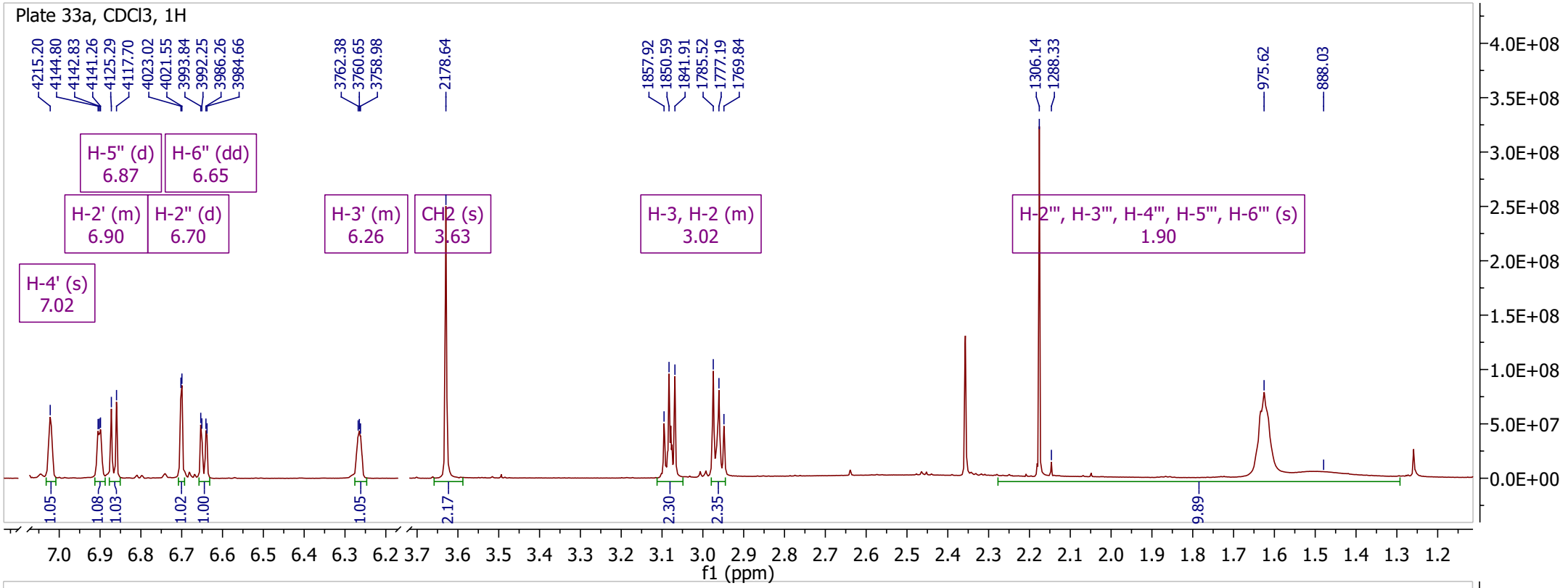
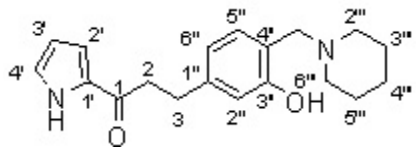


Plate 33a, CDCl3, 1H
4215.20
4144.80
4142.83
4141.26
4125.29
4117.70
4023.02
4021.55
3993.84
3992.25
3986.26
3984.66
3762.38
3760.65
3758.98
2178.64
1857.92
1850.59
1841.91
1785.52
1777.19
1769.84
1306.14
1288.33
975.62
888.03
H-5" (d)
6.87
H-6" (dd)
6.65
H-2' (m)
6.90
H-2" (d)
6.70
H-3' (m)
6.26
CH2 (s)
3.63
H-3, H-2 (m)
3.02
H-2‴, H-3‴, H-4‴, H-5‴, H-6‴ (s)
1.90
H-4' (s)
7.02
1.05
1.08
1.03
1.02
1.00
1.05
2.17
2.30
2.35
9.89
f1 (ppm)



62

f1 (ppm)

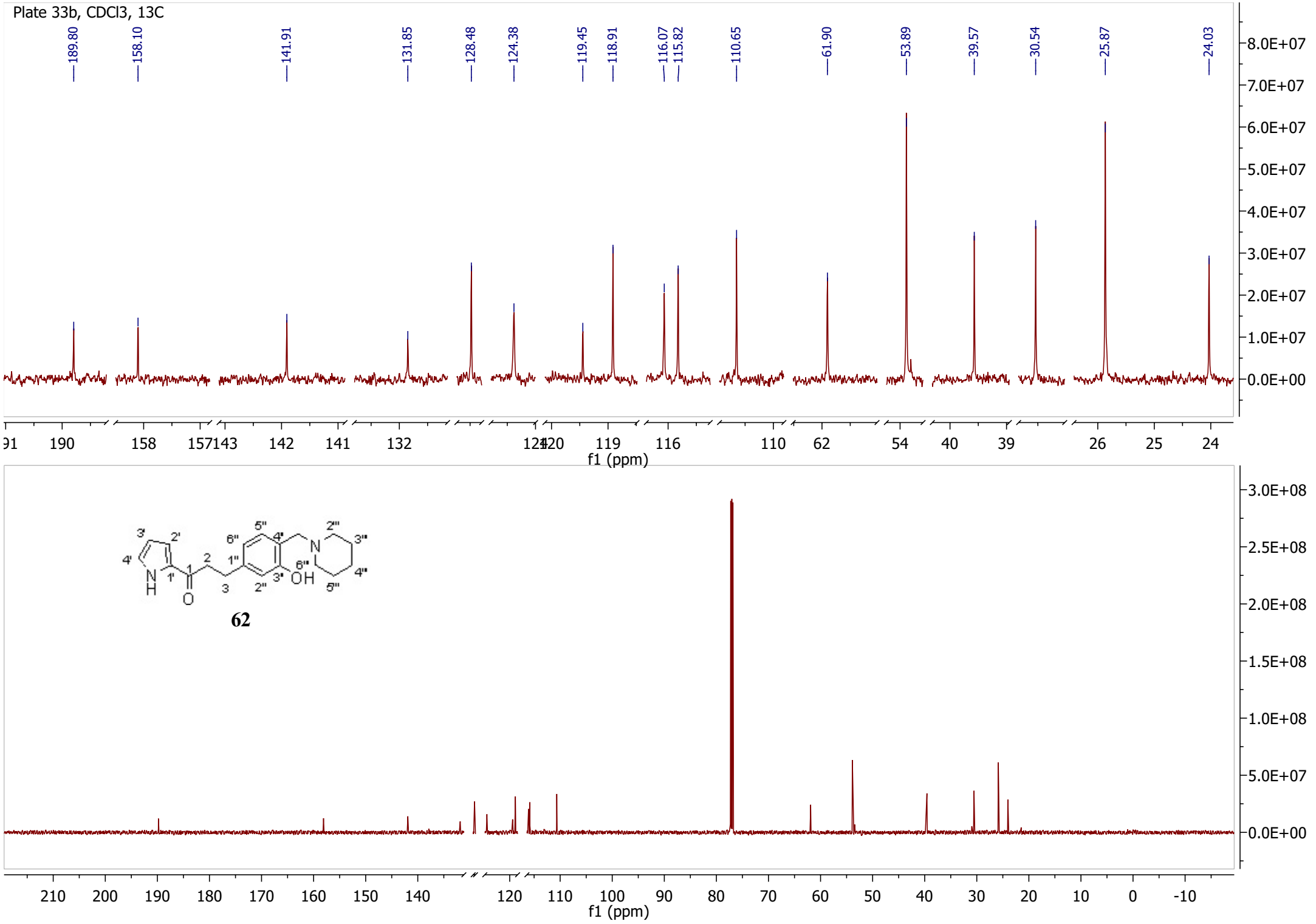


Plate 33b, CDCl3, 13C
189.80
158.10
141.91
131.85
128.48
124.38
119.45
118.91
116.07
115.82
110.65
61.90
53.89
39.57
30.54
25.87
24.03
f1 (ppm)
f1 (ppm)

62

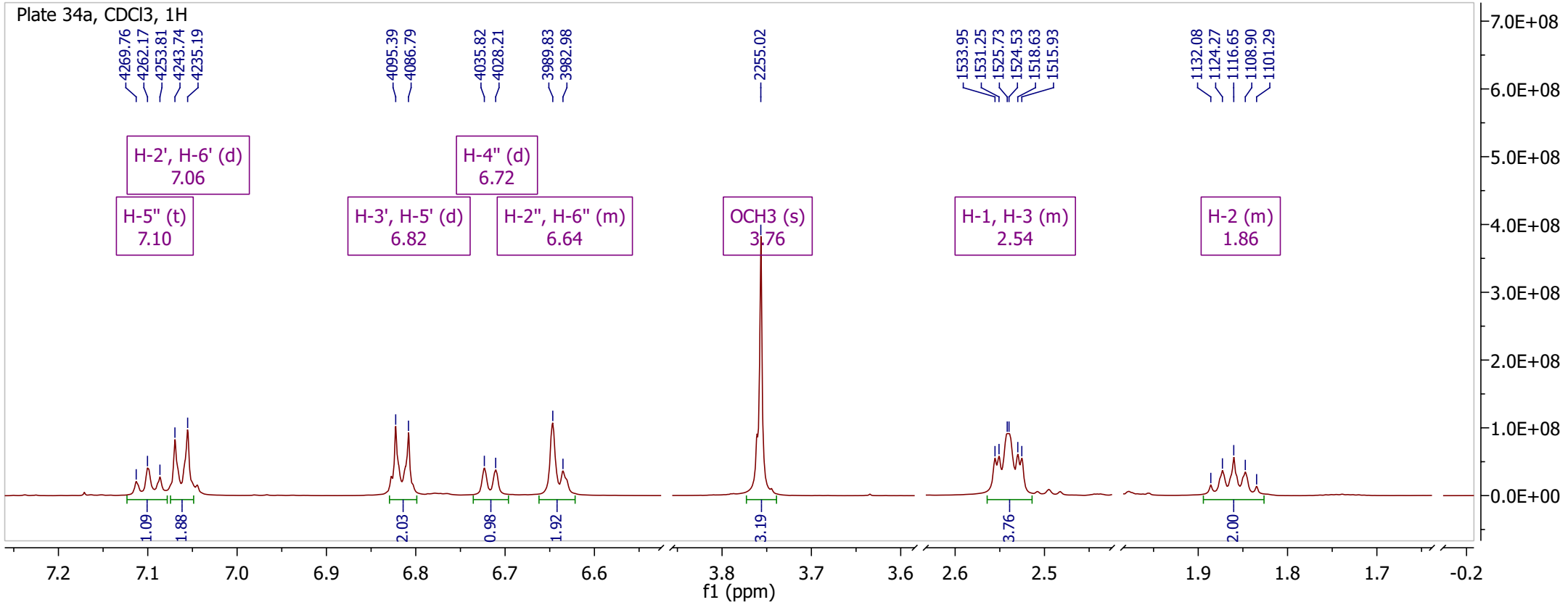
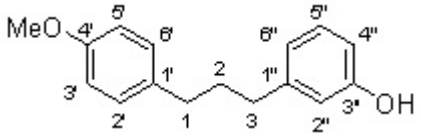


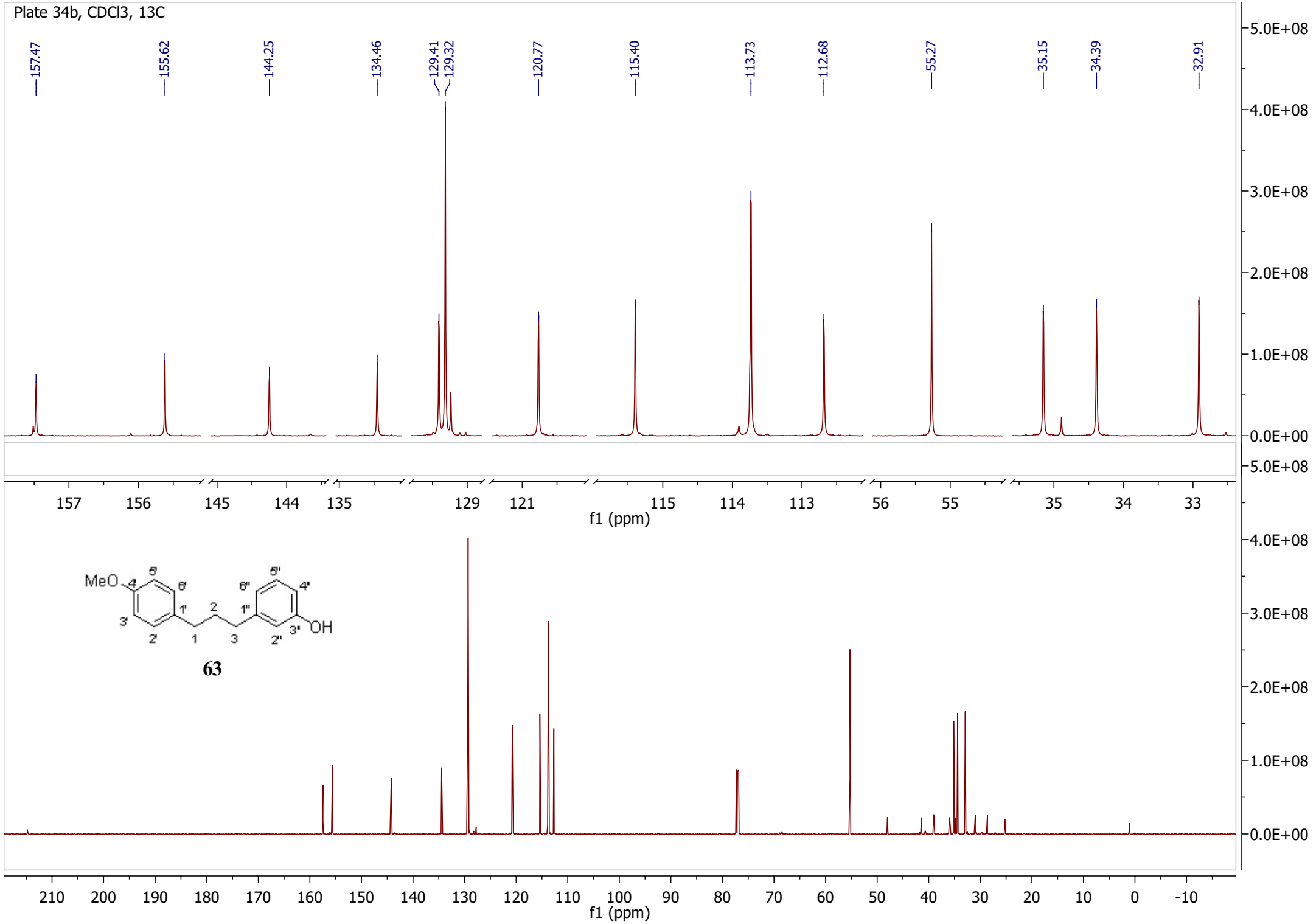
Plate 34a, CDCl3, 1H
4269.76
4262.17
4253.81
4243.74
4235.19
4095.39
4086.79
4035.82
4028.21
3989.83
3982.98
2255.02
1533.95
1531.25
1525.73
1524.53
1518.63
1515.93
1132.08
1124.27
1116.65
1108.90
1101.29
H-2', H-6' (d)
7.06
H-4" (d)
6.72
H-5" (t)
7.10
H-3', H-5' (d)
6.82
H-2", H-6" (m)
6.64
OCH3 (s)
3.76
H-1, H-3 (m)
2.54
H-2 (m)
1.86
1.09
1.88
2.03
0.98
1.92
3.19
3.76
2.00
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.2
7.1
7.0
6.9
6.8
6.7
6.6
3.8
3.7
3.6
2.6
2.5
1.9
1.8
1.7
-0.2
f1 (ppm)


MeO
OH

63

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Plate 34b, CDCl3, 13C



63

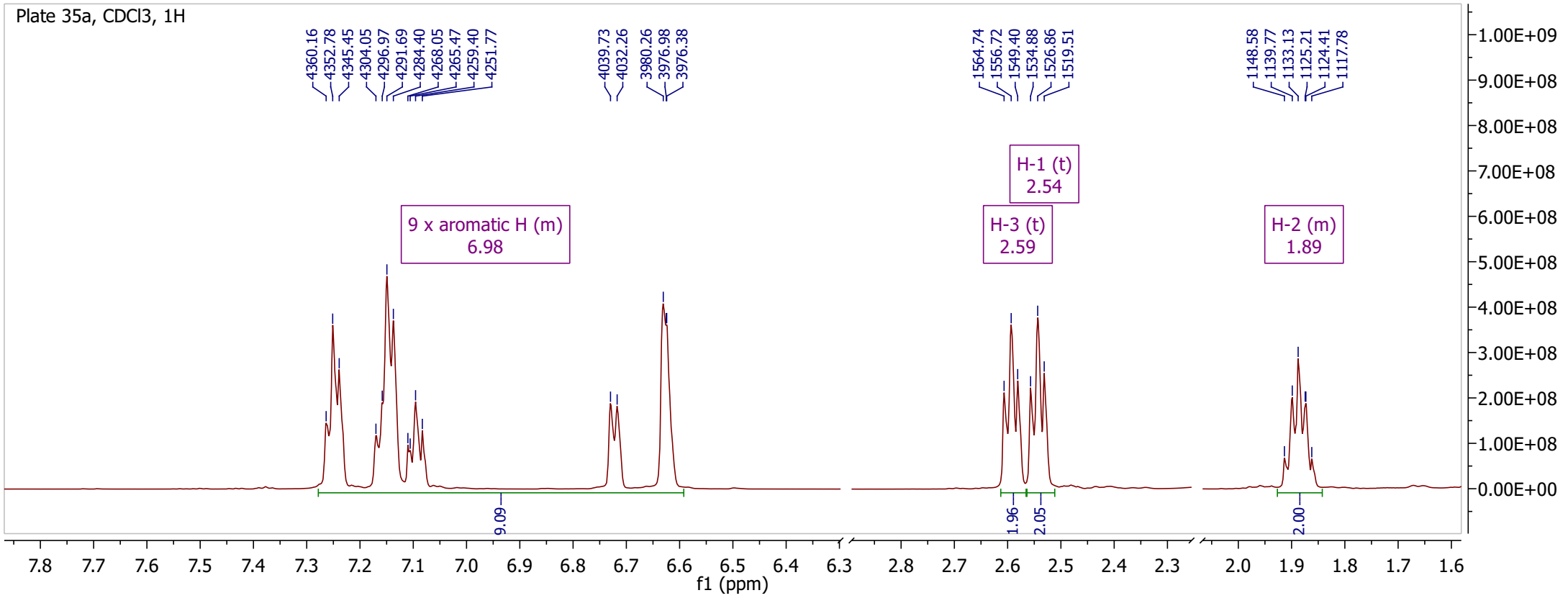
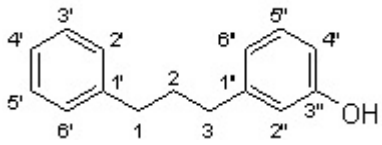


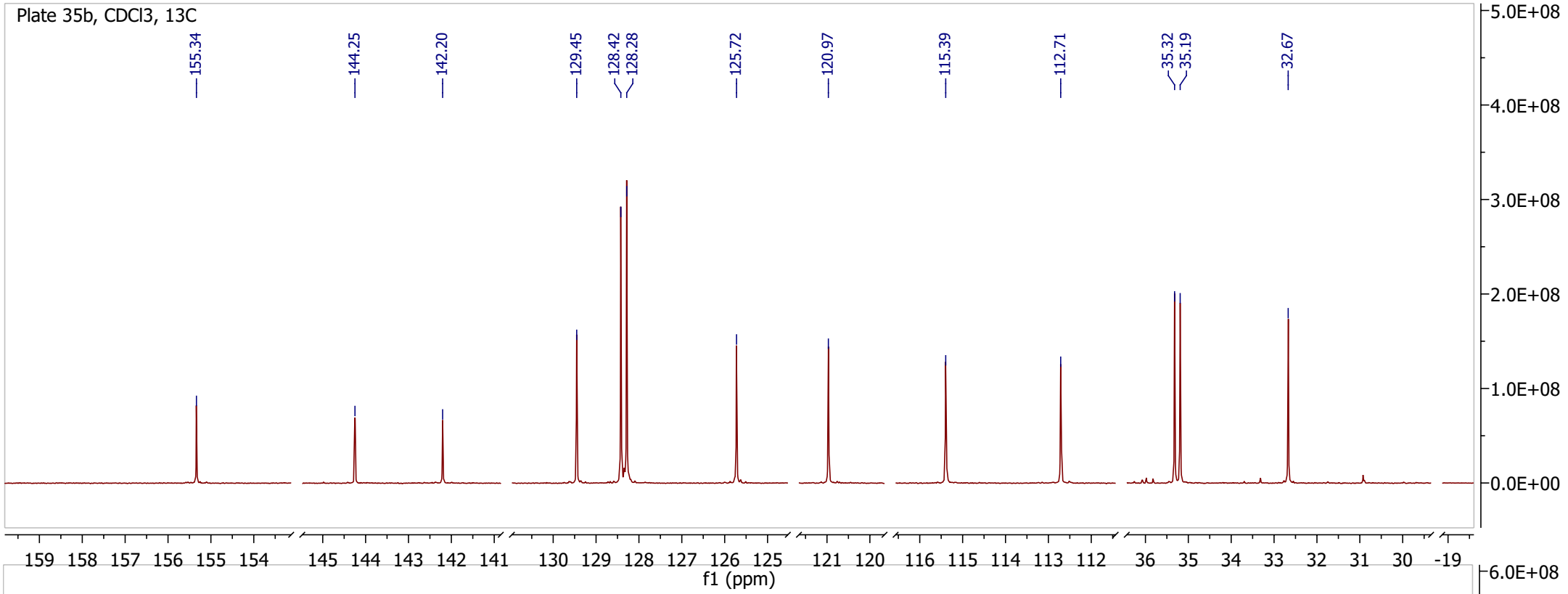
Plate 35a, CDCl3, 1H
4360.16
4352.78
4345.45
4304.05
4296.97
4291.69
4284.40
4268.05
4265.47
4259.40
4251.77
4039.73
4032.26
3980.26
3976.98
3976.38
1564.74
1556.72
1549.40
1534.88
1526.86
1519.51
1148.58
1139.77
1133.13
1125.21
1124.41
1117.78
9 x aromatic H (m)
6.98
H-1 (t)
2.54
H-3 (t)
2.59
H-2 (m)
1.89
9.09
1.96
2.05
2.00
f1 (ppm)

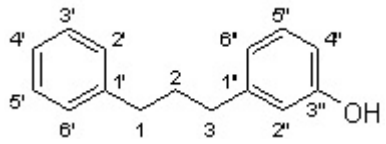

OH

112

f1 (ppm)

Plate 35b, CDCl3, 13C





112

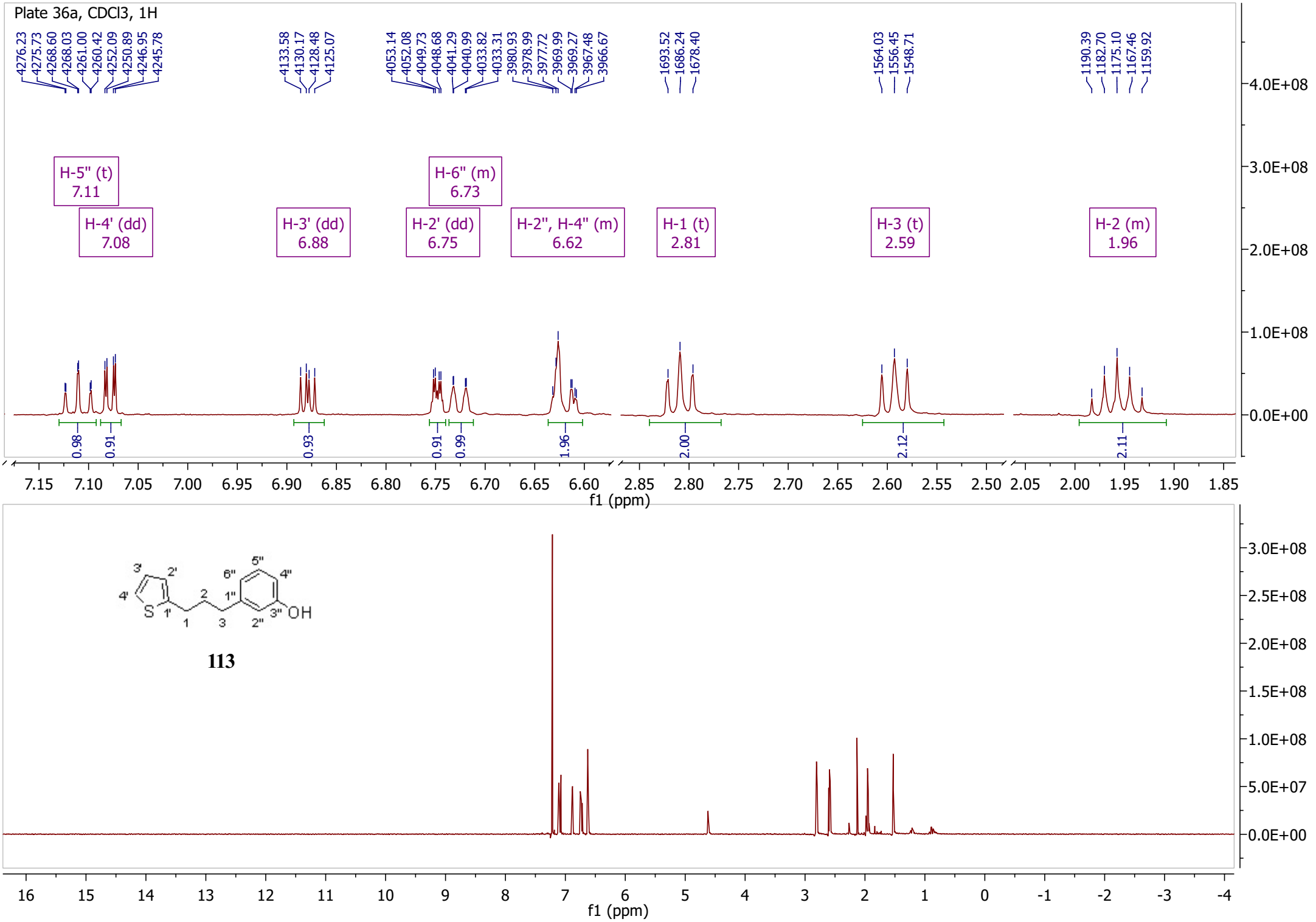


Plate 36a, CDCl3, 1H
4276.23
4275.73
4268.60
4268.03
4261.00
4260.42
4252.09
4250.89
4246.95
4245.78
4133.58
4130.17
4128.48
4125.07
4053.14
4052.08
4049.73
4048.68
4041.29
4040.99
4033.82
4033.31
3980.93
3978.99
3977.72
3969.99
3969.27
3967.48
3966.67
1693.52
1686.24
1678.40
1564.03
1556.45
1548.71
1190.39
1182.70
1175.10
1167.46
1159.92
H-5" (t)
7.11
H-4' (dd)
7.08
H-3' (dd)
6.88
H-6" (m)
6.73
H-2' (dd)
6.75
H-2", H-4" (m)
6.62
H-1 (t)
2.81
H-3 (t)
2.59
H-2 (m)
1.96
0.98
0.91
0.93
0.91
0.99
1.96
2.00
2.12
2.11
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70 6.65 6.60 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.05 2.00 1.95 1.90 1.85
f1 (ppm)
3
2'
4'
S
1'
1
2
3
6"
5"
4"
1"
2"
3"
OH
113
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

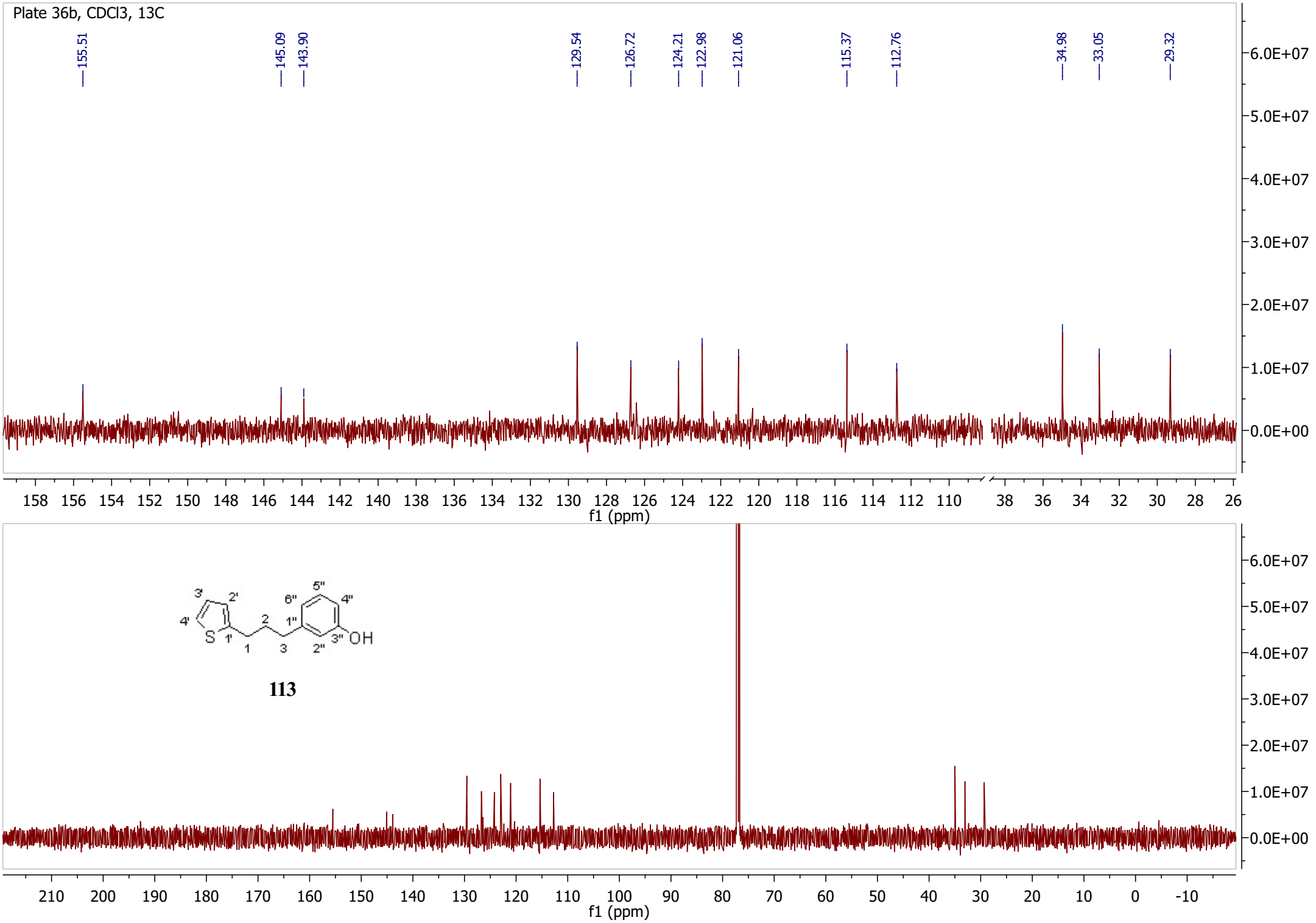
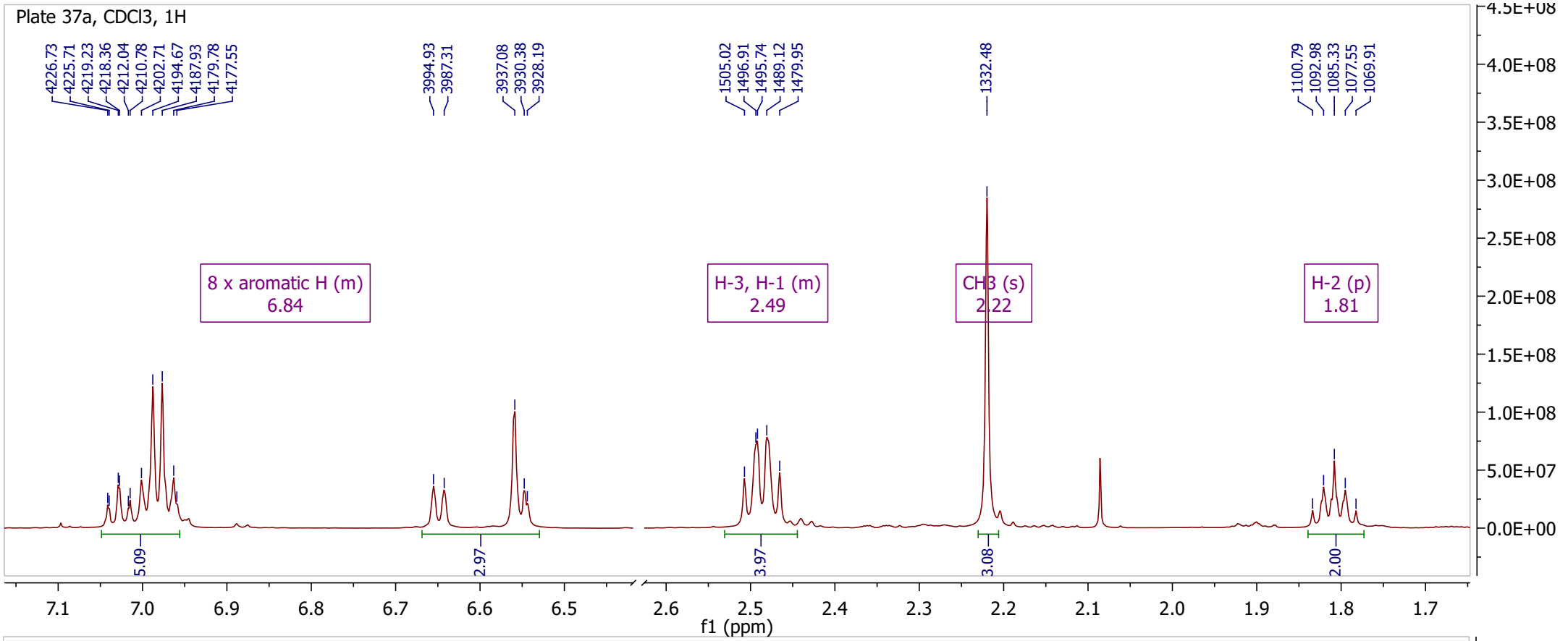
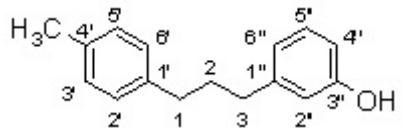


Plate 36b, CDCl3, 13C
155.51
145.09
143.90
129.54
126.72
124.21
122.98
121.06
115.37
112.76
34.98
33.05
29.32
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
158 156 154 152 150 148 146 144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112 110 38 36 34 32 30 28 26
f1 (ppm)
3'
2'
4'
S
1'
2
1
3
1"
6"
5"
4"
3"
OH
2"
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

113

Plate 37a, CDCl3, 1H





114

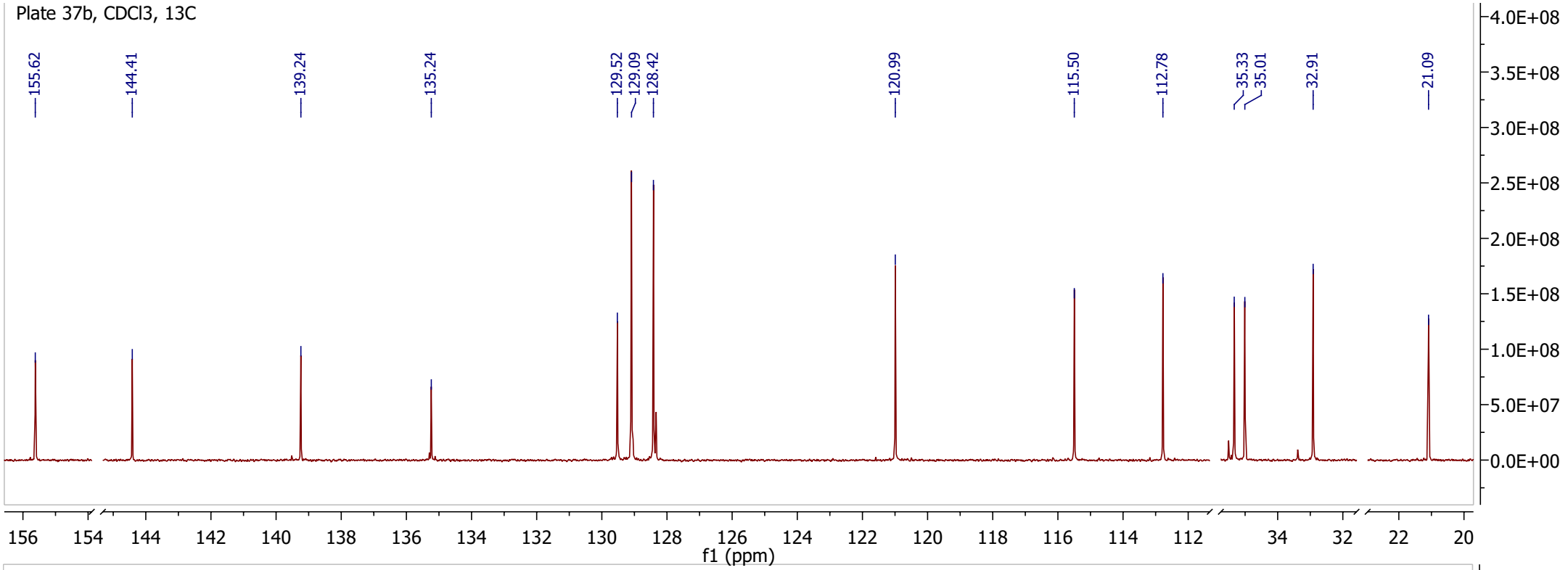
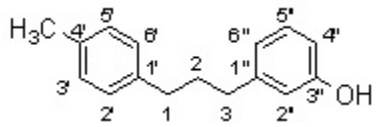


Plate 37b, CDCl3, 13C
155.62
144.41
139.24
135.24
129.52
129.09
128.42
120.99
115.50
112.78
35.33
35.01
32.91
21.09
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
156 154 144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112 34 32 22 20
f1 (ppm)


H3C
OH

114

2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

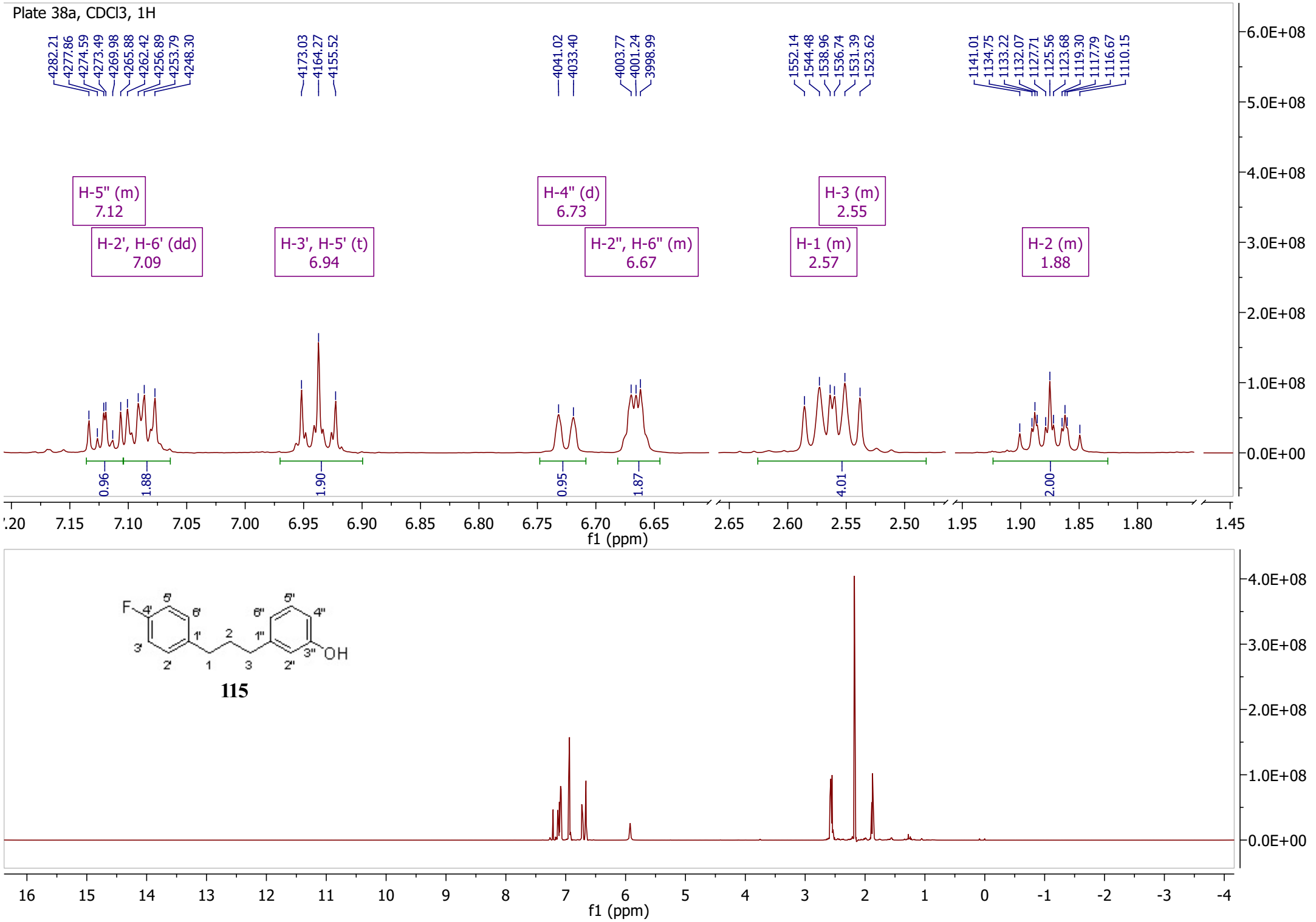


Plate 38a, CDCl3, 1H
4282.21
4277.86
4274.59
4273.49
4269.98
4265.88
4262.42
4256.89
4253.79
4248.30
4173.03
4164.27
4155.52
4041.02
4033.40
4003.77
4001.24
3998.99
1552.14
1544.48
1538.96
1536.74
1531.39
1523.62
1141.01
1134.75
1133.22
1132.07
1127.71
1125.56
1123.68
1119.30
1117.79
1116.67
1110.15
H-5" (m)
7.12
H-2', H-6' (dd)
7.09
H-3', H-5' (t)
6.94
H-4" (d)
6.73
H-2", H-6" (m)
6.67
H-3 (m)
2.55
H-1 (m)
2.57
H-2 (m)
1.88
0.96
1.88
1.90
0.95
1.87
4.01
2.00
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.20
7.15
7.10
7.05
7.00
6.95
6.90
6.85
6.80
6.75
6.70
6.65
2.65
2.60
2.55
2.50
1.95
1.90
1.85
1.80
1.45
f1 (ppm)
F
OH
115
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

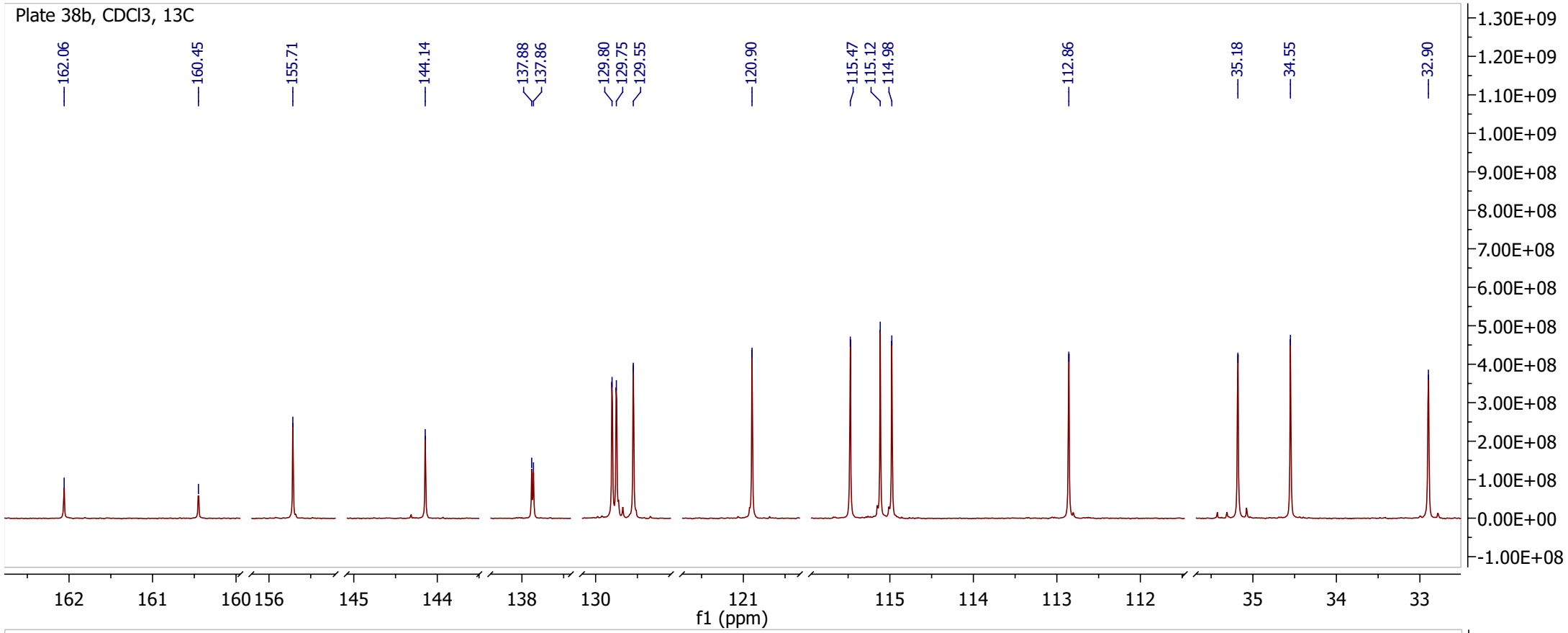
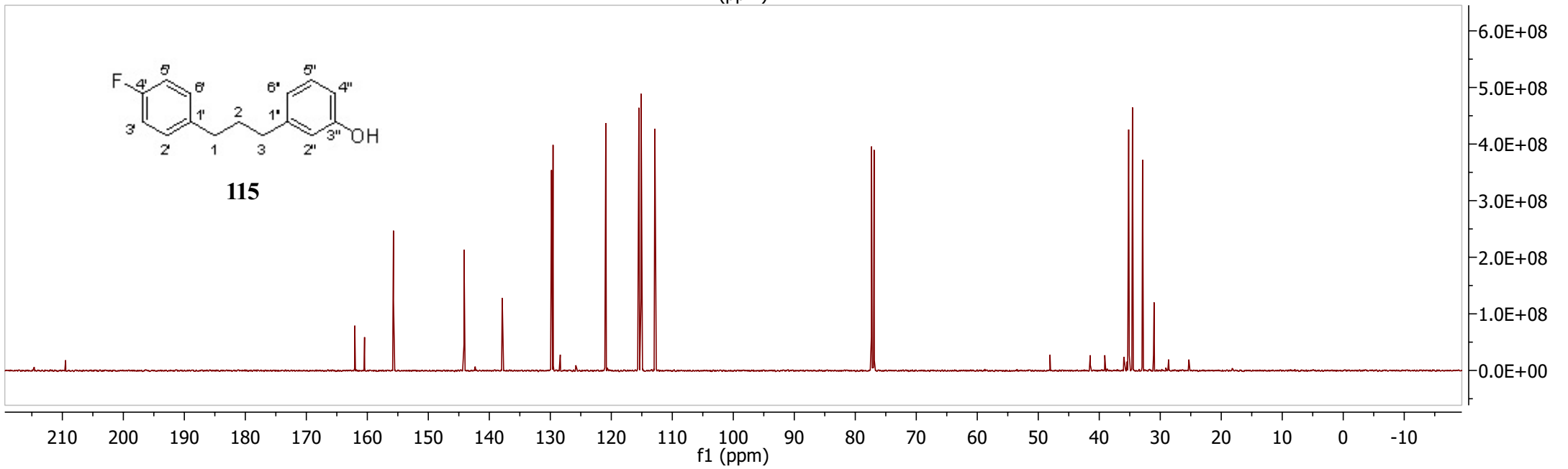


Plate 38b, CDCl3, 13C
162.06
160.45
155.71
144.14
137.88
137.86
129.80
129.75
129.55
120.90
115.47
115.12
114.98
112.86
35.18
34.55
32.90
f1 (ppm)


F
OH
f1 (ppm)

115

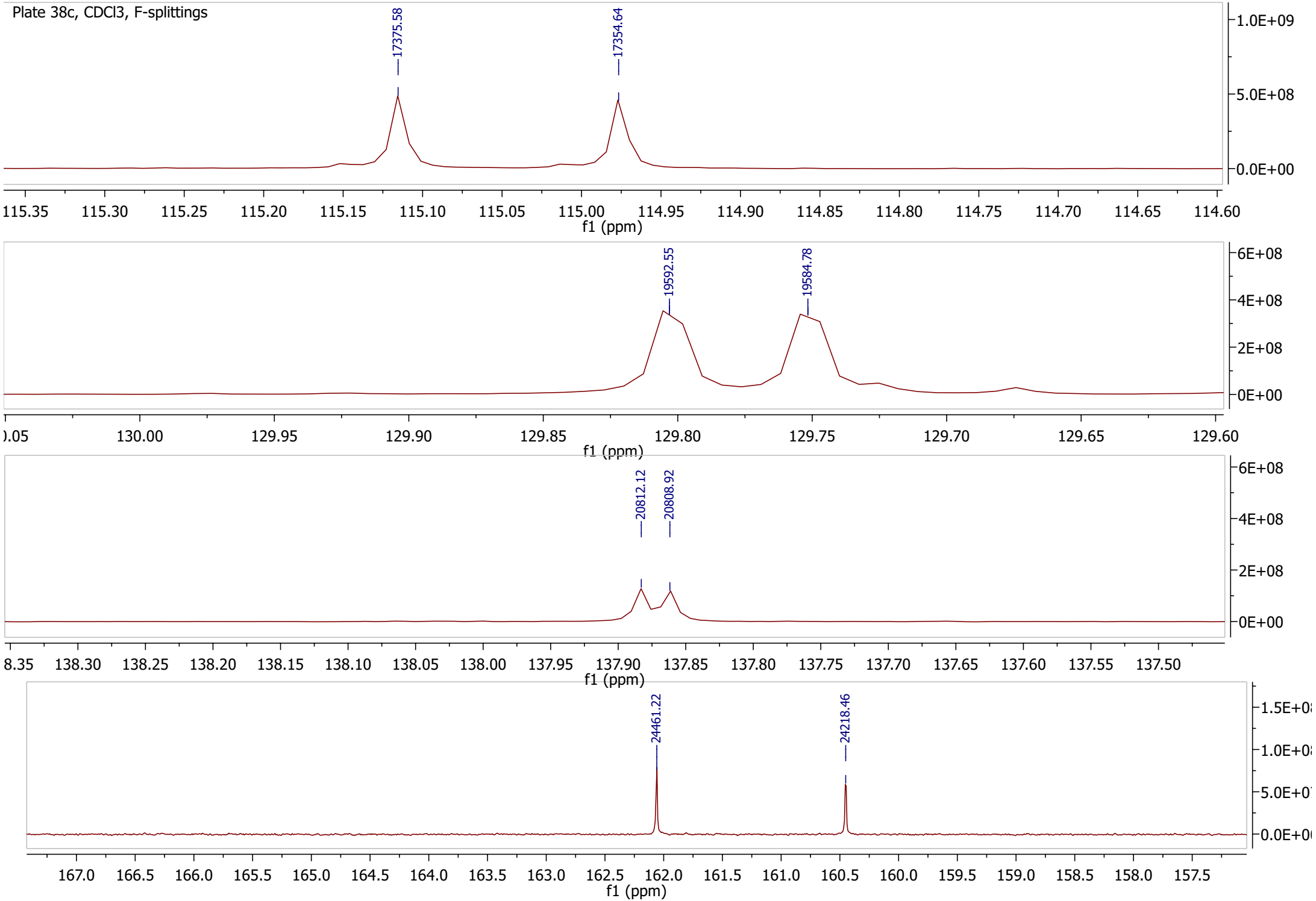
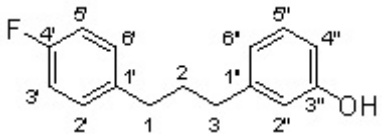


Plate 38c, CDCl3, F-splittings
17375.58
17354.64
1.0E+09
5.0E+08
0.0E+00
115.35 115.30 115.25 115.20 115.15 115.10 115.05 115.00 114.95 114.90 114.85 114.80 114.75 114.70 114.65 114.60
f1 (ppm)
19592.55
19584.78
6E+08
4E+08
2E+08
0E+00
130.00 129.95 129.90 129.85 129.80 129.75 129.70 129.65 129.60
f1 (ppm)
20812.12
20808.92
6E+08
4E+08
2E+08
0E+00
138.30 138.25 138.20 138.15 138.10 138.05 138.00 137.95 137.90 137.85 137.80 137.75 137.70 137.65 137.60 137.55 137.50
f1 (ppm)
24461.22
24218.46
1.5E+08
1.0E+08
5.0E+07
0.0E+00
167.0 166.5 166.0 165.5 165.0 164.5 164.0 163.5 163.0 162.5 162.0 161.5 161.0 160.5 160.0 159.5 159.0 158.5 158.0 157.5
f1 (ppm)

Plate 38d, CDCl3, 19F

-117.88



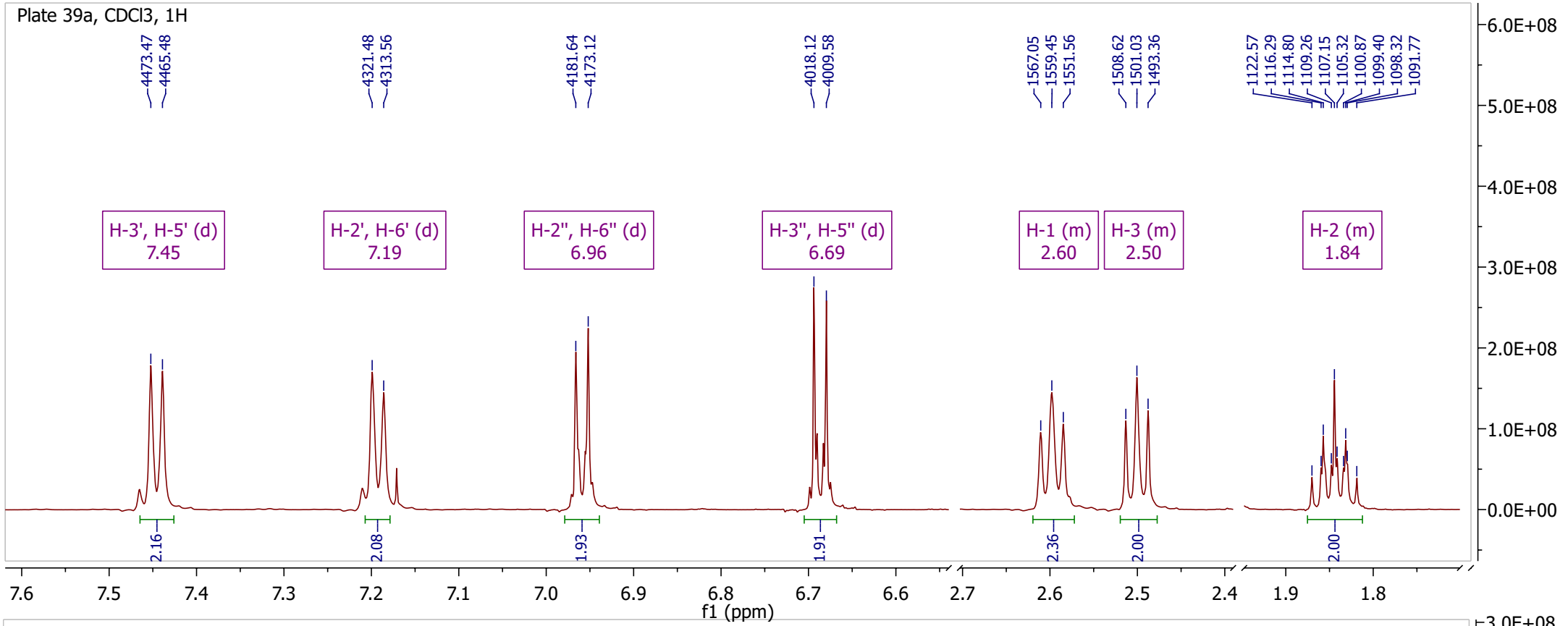
115

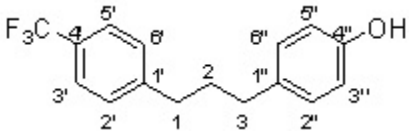
8.0E+08
7.5E+08
7.0E+08
6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
-1.0E+08

00 50 0 -50 -100 -150 -200 -250 -300

f1 (ppm)

Plate 39a, CDCl3, 1H





116

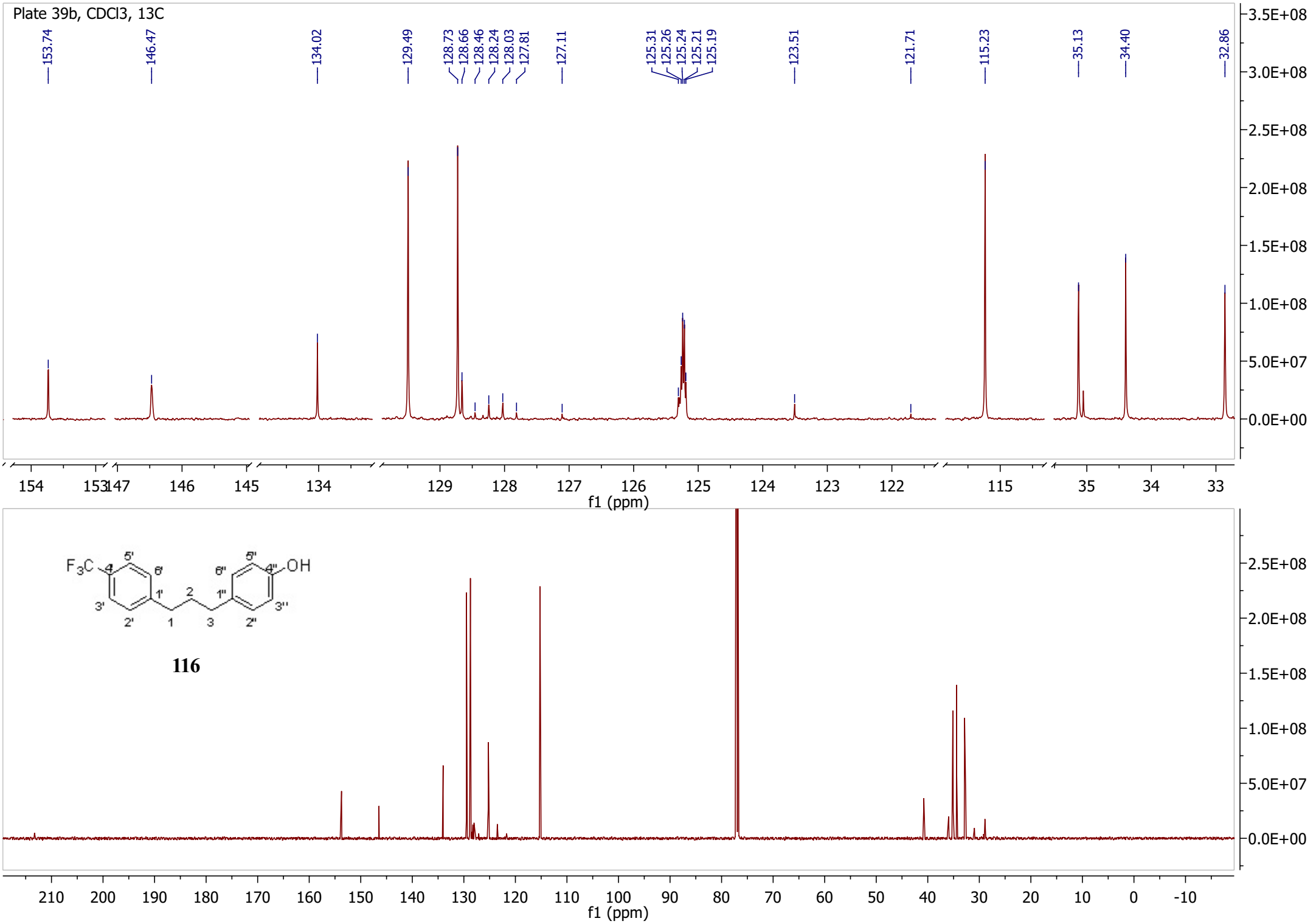


Plate 39b, CDCl3, 13C
153.74
146.47
134.02
129.49
128.73
128.66
128.46
128.24
128.03
127.81
127.11
125.31
125.26
125.24
125.21
125.19
123.51
121.71
115.23
35.13
34.40
32.86
f1 (ppm)
F3C
OH
116
f1 (ppm)

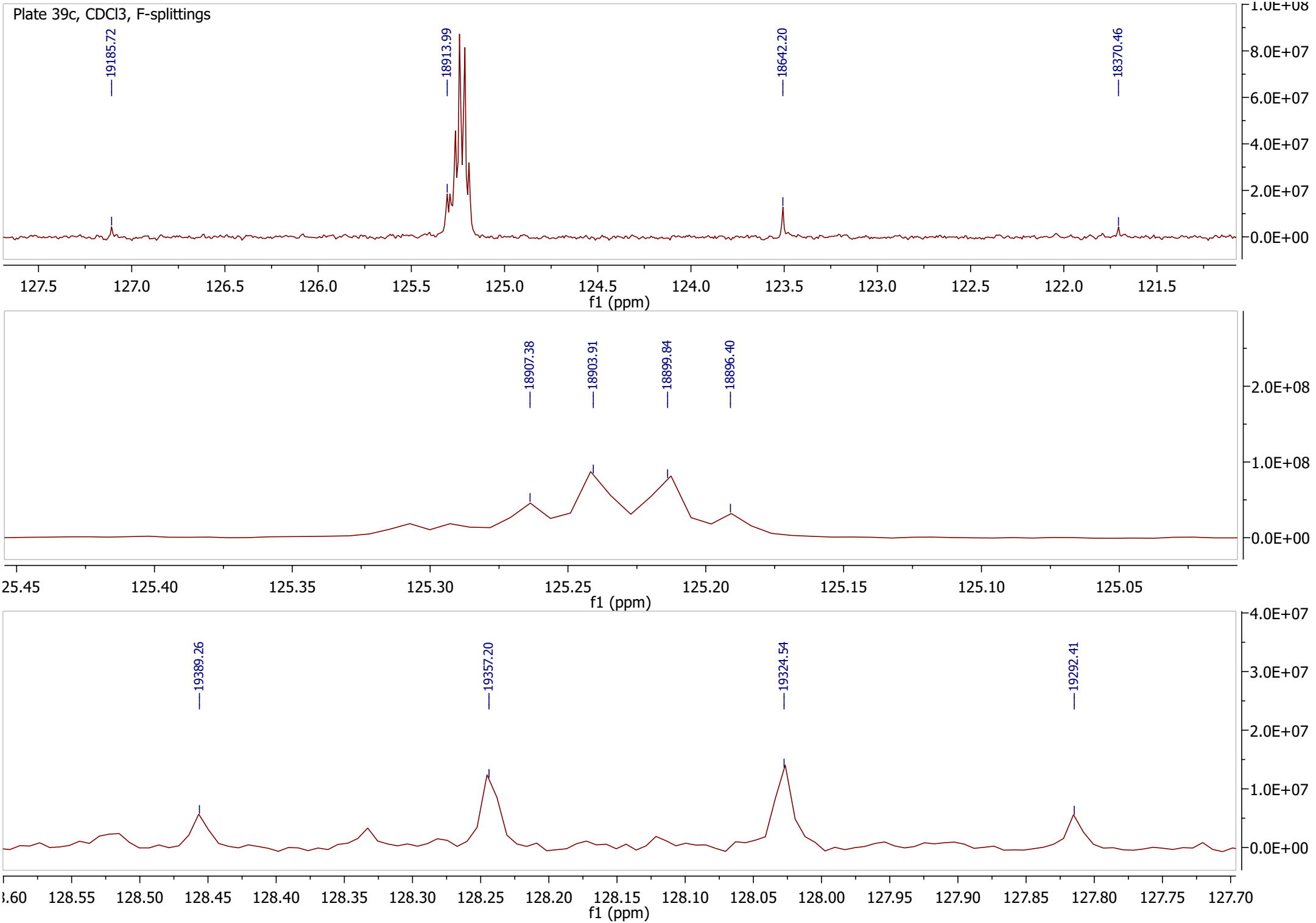
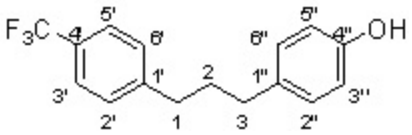


Plate 39c, CDCl3, F-splittings
19185.72
18913.99
18642.20
18370.46
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
127.5
127.0
126.5
126.0
125.5
125.0
124.5
124.0
123.5
123.0
122.5
122.0
121.5
f1 (ppm)
18907.38
18903.91
18899.84
18896.40
2.0E+08
1.0E+08
0.0E+00
25.45
125.40
125.35
125.30
125.25
125.20
125.15
125.10
125.05
f1 (ppm)
19389.26
19357.20
19324.54
19292.41
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
.60
128.55
128.50
128.45
128.40
128.35
128.30
128.25
128.20
128.15
128.10
128.05
128.00
127.95
127.90
127.85
127.80
127.75
127.70
f1 (ppm)

Plate 39d, CDCl3, 19F

-62.25



116

6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07

00 50 0 -50 -100 -150 -200 -250 -300

f1 (ppm)

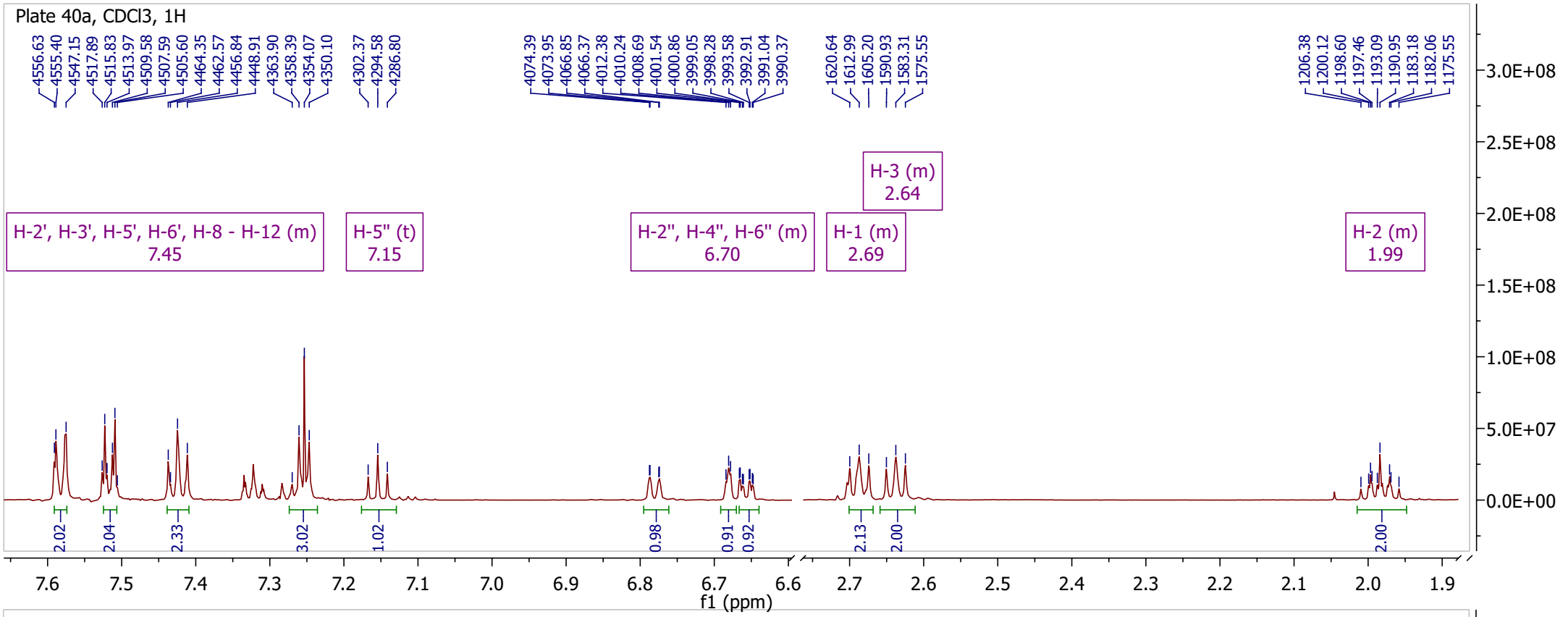
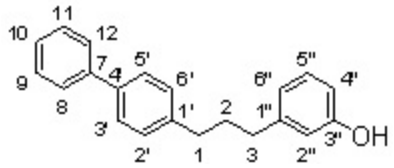


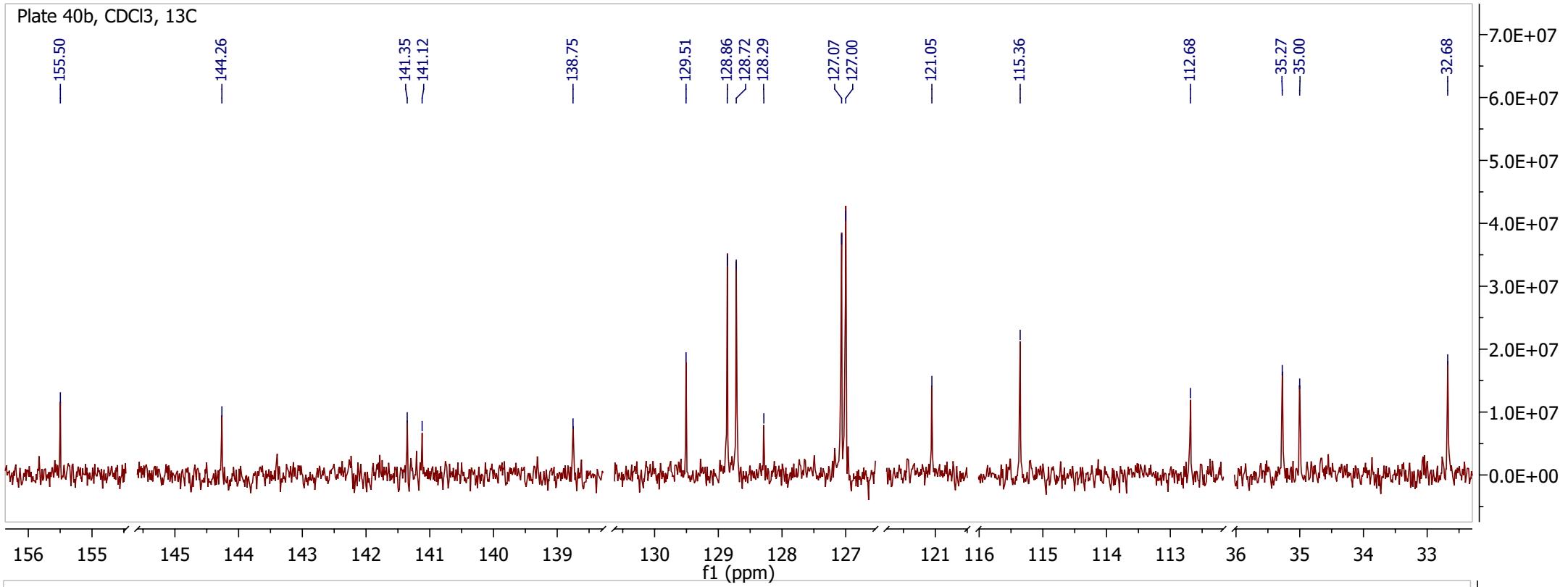
Plate 40a, CDCl3, 1H
H-2', H-3', H-5', H-6', H-8 - H-12 (m)
7.45
H-5" (t)
7.15
H-2", H-4", H-6" (m)
6.70
H-3 (m)
2.64
H-1 (m)
2.69
H-2 (m)
1.99
f1 (ppm)

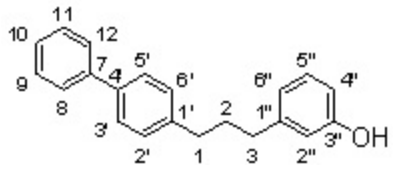

OH

117

f1 (ppm)

Plate 40b, CDCl3, 13C





117

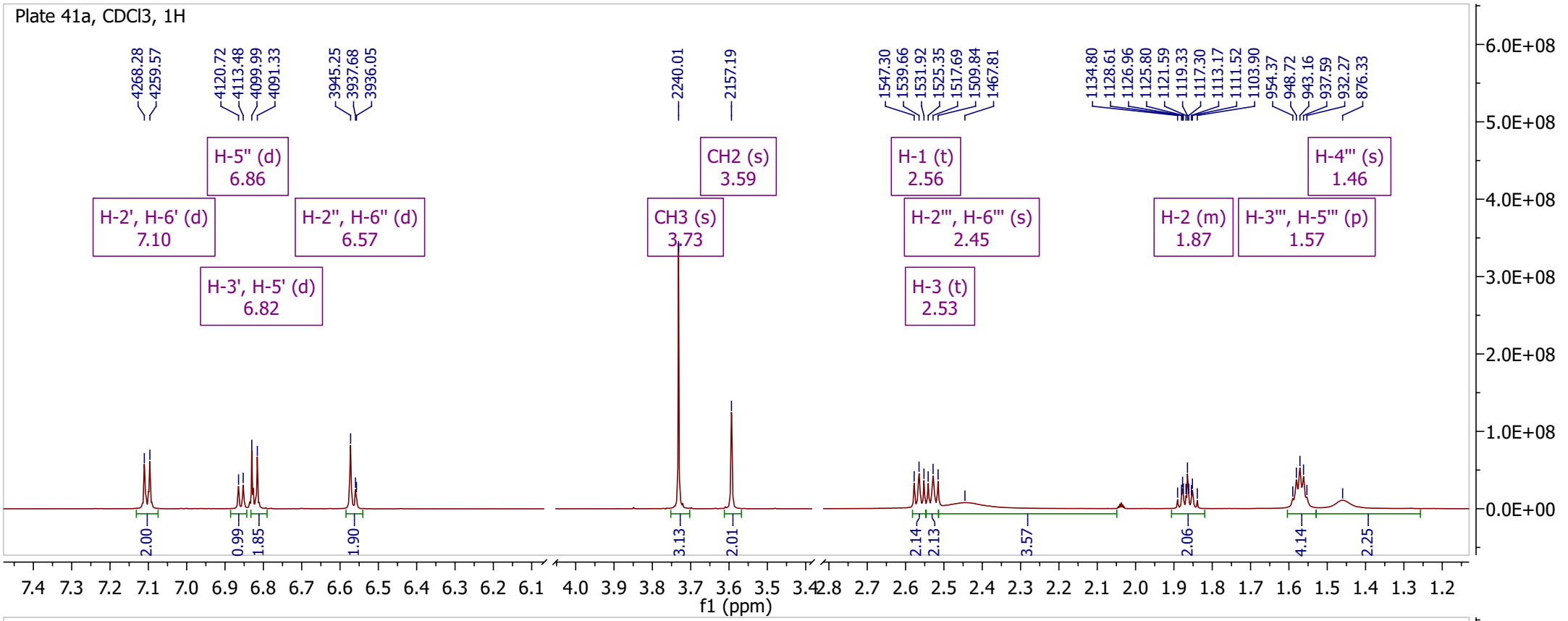
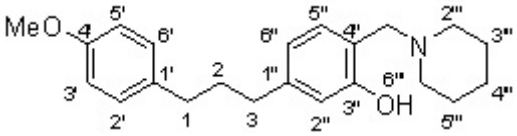


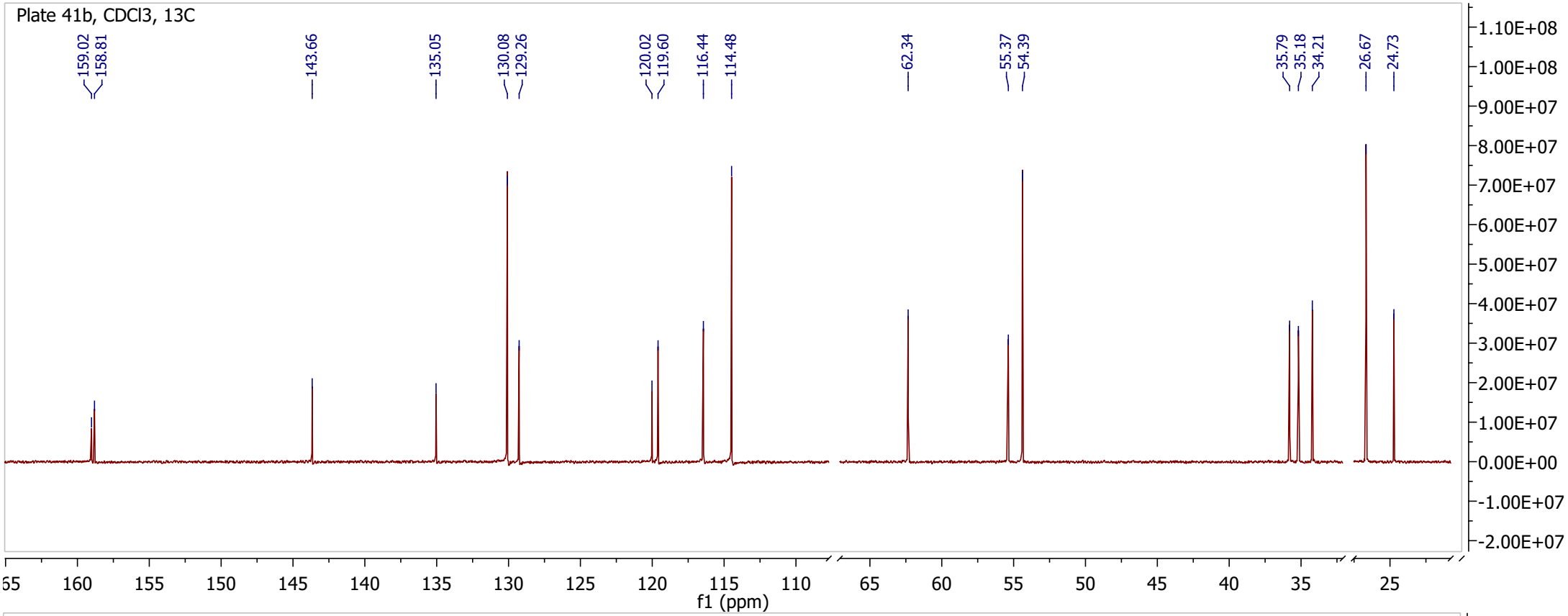
Plate 41a, CDCl3, 1H
4268.28
4259.57
4120.72
4113.48
4099.99
4091.33
3945.25
3937.68
3936.05
2240.01
2157.19
1547.30
1539.66
1531.92
1525.35
1517.69
1509.84
1467.81
1134.80
1128.61
1126.96
1125.80
1121.59
1119.33
1117.30
1113.17
1111.52
1103.90
954.37
948.72
943.16
937.59
932.27
876.33
H-5" (d)
6.86
H-2', H-6' (d)
7.10
H-2", H-6" (d)
6.57
H-3', H-5' (d)
6.82
CH2 (s)
3.59
CH3 (s)
3.73
H-1 (t)
2.56
H-2"', H-6"' (s)
2.45
H-3 (t)
2.53
H-2 (m)
1.87
H-3"', H-5"' (p)
1.57
H-4"' (s)
1.46
2.00
0.99
1.85
1.90
3.13
2.01
2.14
2.13
3.57
2.06
4.14
2.25
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
f1 (ppm)

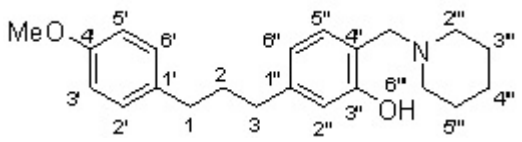

MeO
OH
N

64

3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

Plate 41b, CDCl3, 13C





64

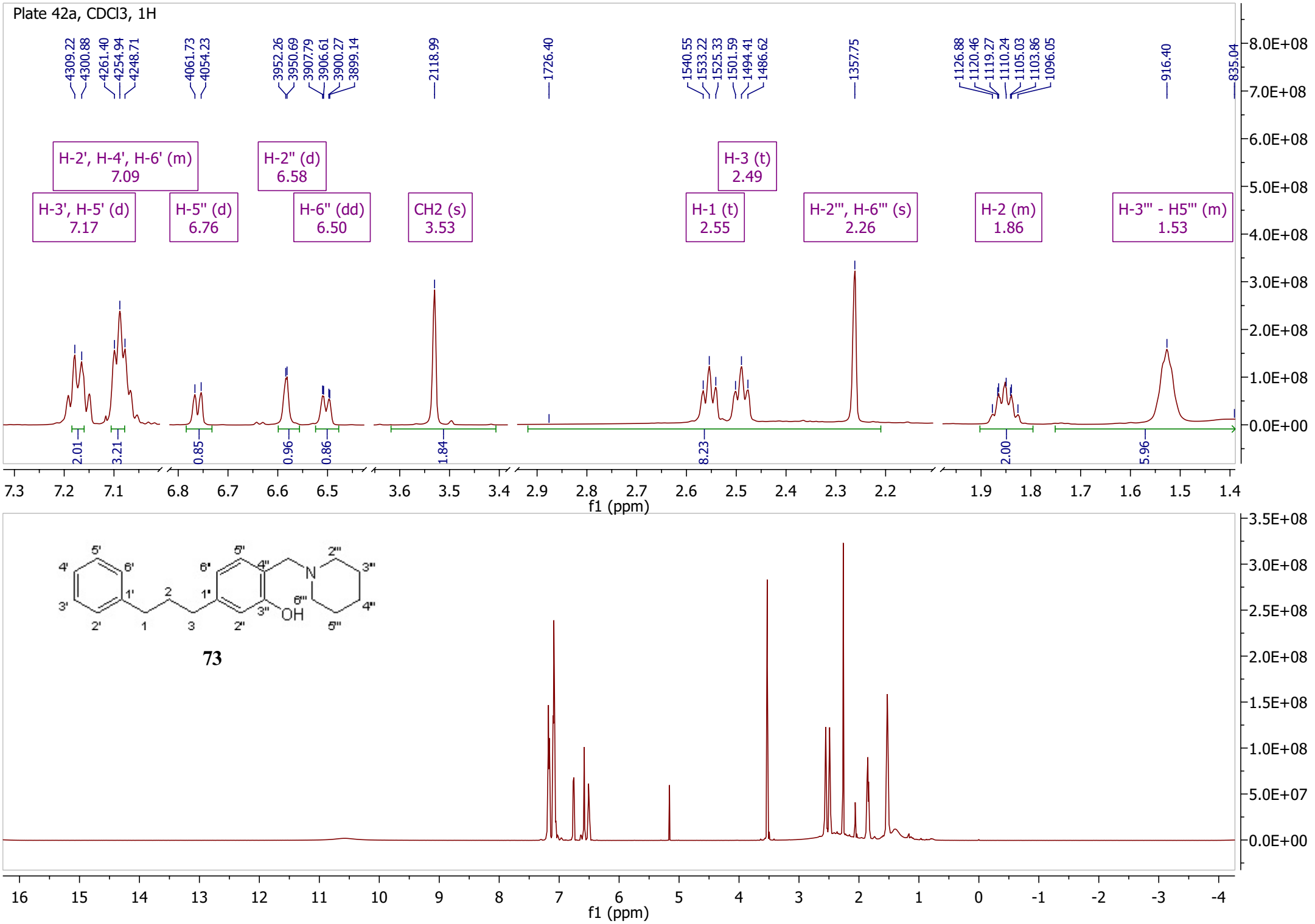


Plate 42a, CDCl3, 1H
4309.22
4300.88
4261.40
4254.94
4248.71
4061.73
4054.23
3952.26
3950.69
3907.79
3906.61
3900.27
3899.14
2118.99
1726.40
1540.55
1533.22
1525.33
1501.59
1494.41
1486.62
1357.75
1126.88
1120.46
1119.27
1110.24
1105.03
1103.86
1096.05
916.40
835.04
H-2', H-4', H-6' (m)
7.09
H-2" (d)
6.58
H-3 (t)
2.49
H-3', H-5' (d)
7.17
H-5" (d)
6.76
H-6" (dd)
6.50
CH2 (s)
3.53
H-1 (t)
2.55
H-2"', H-6"' (s)
2.26
H-2 (m)
1.86
H-3"' - H5"' (m)
1.53
2.01
3.21
0.85
0.96
0.86
1.84
8.23
2.00
5.96
f1 (ppm)
f1 (ppm)

5'
4'
6'
1'
2
3'
2'
1
3
5'
6'
4"
2"
3"
N
1'
6"
3"
OH
4"
2'
5"

73

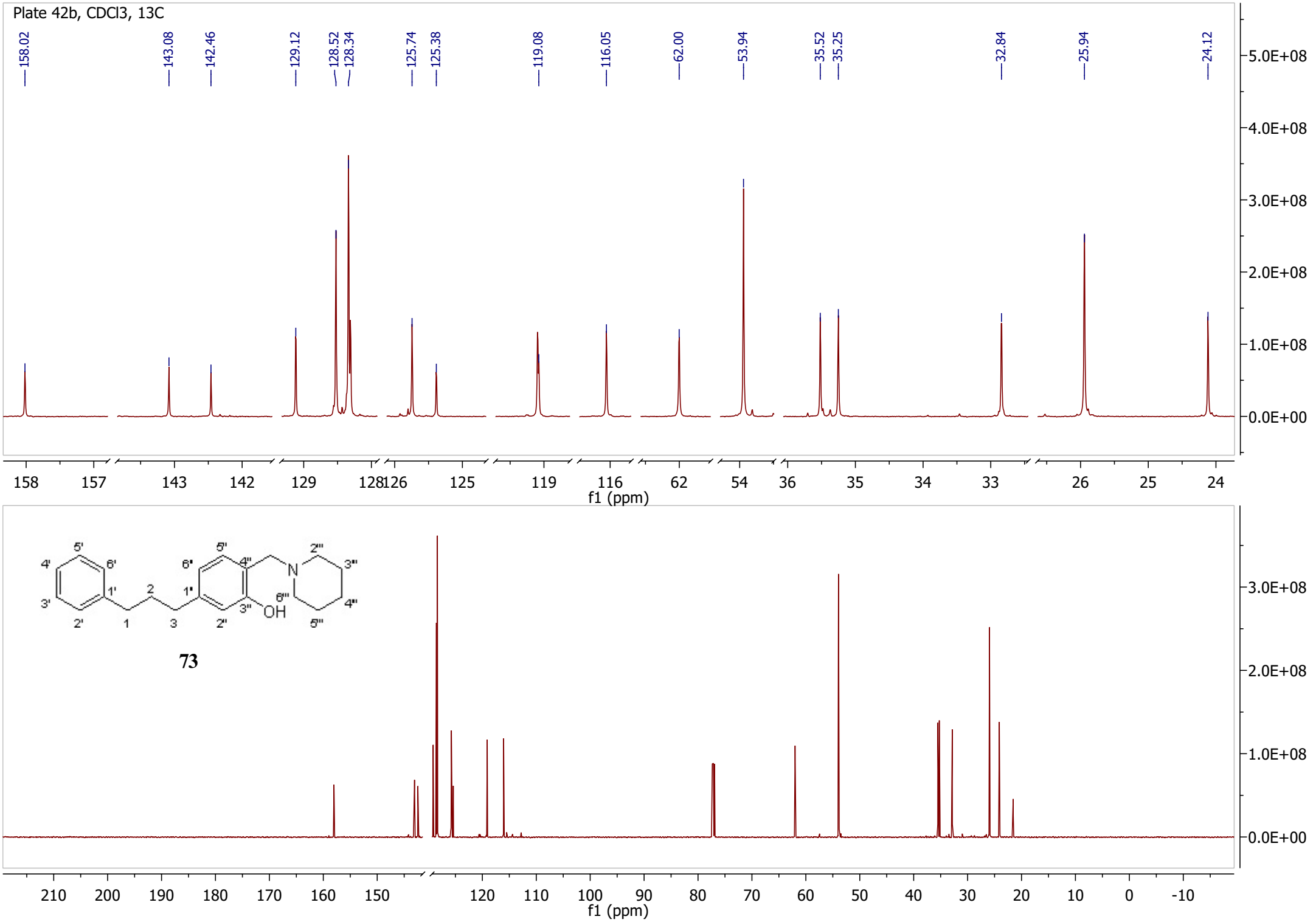
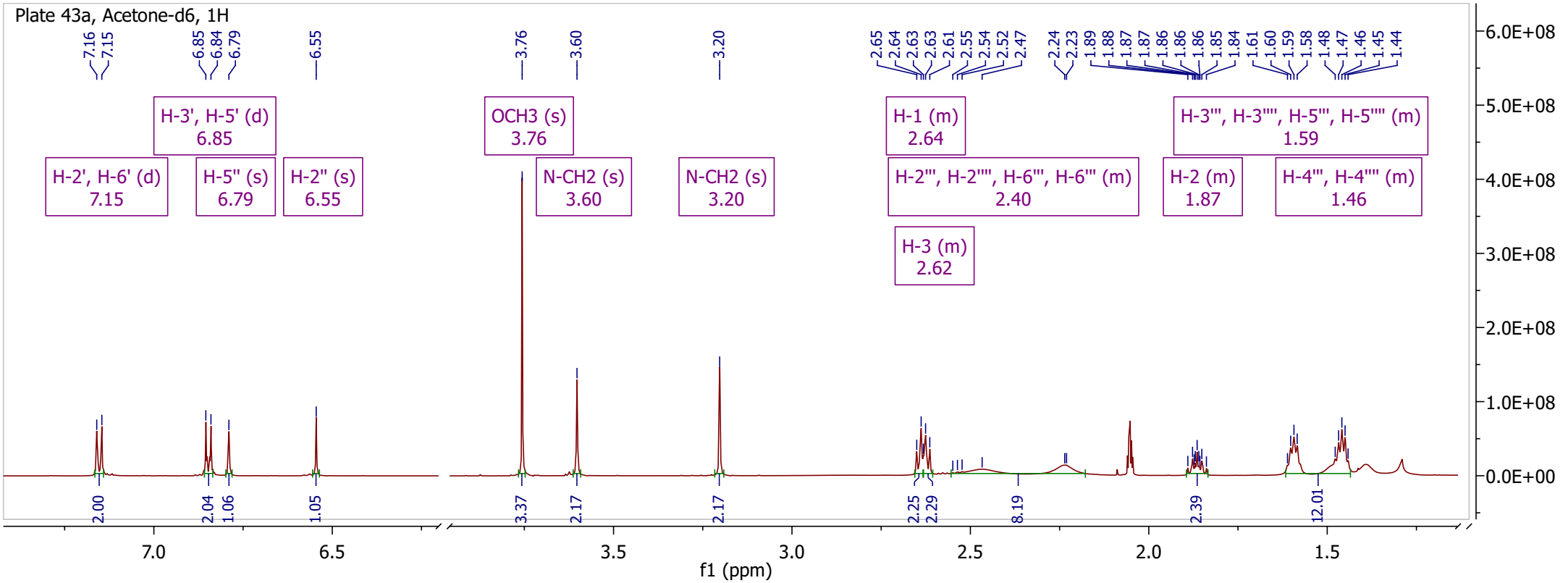
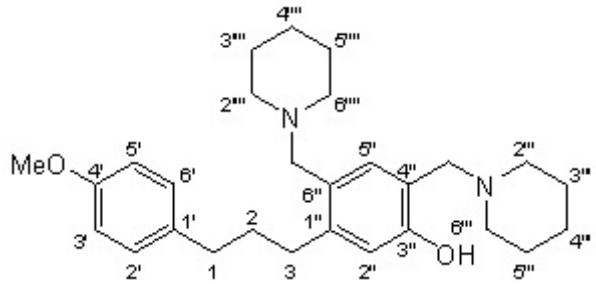


Plate 42b, CDCl3, 13C
158.02
143.08
142.46
129.12
128.52
128.34
125.74
125.38
119.08
116.05
62.00
53.94
35.52
35.25
32.84
25.94
24.12
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
158 157 143 142 129 128 126 125 119 116 62 54 36 35 34 33 26 25 24
f1 (ppm)
5'
4'
6'
1'
2
3'
2'
1
3
5'
6'
4"
2"
3"
N
1'
6"
3"
OH
4"
5"
2'
73
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

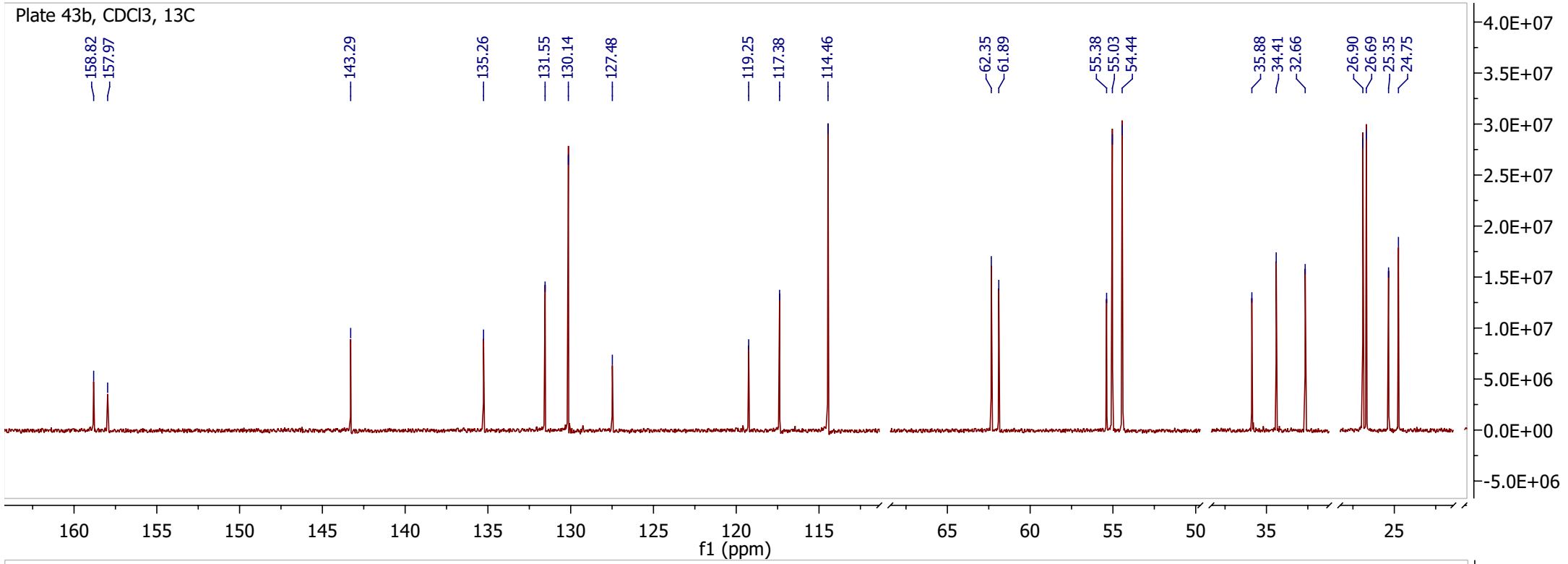
Plate 43a, Acetone-d6, 1H

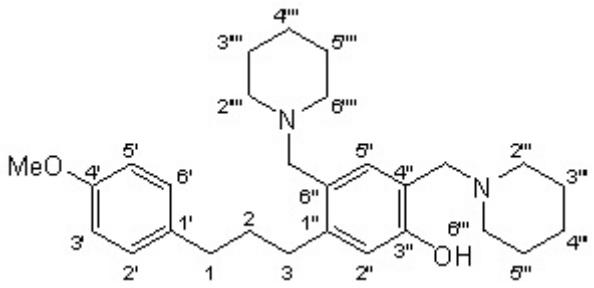




65

Plate 43b, CDCl3, 13C





65

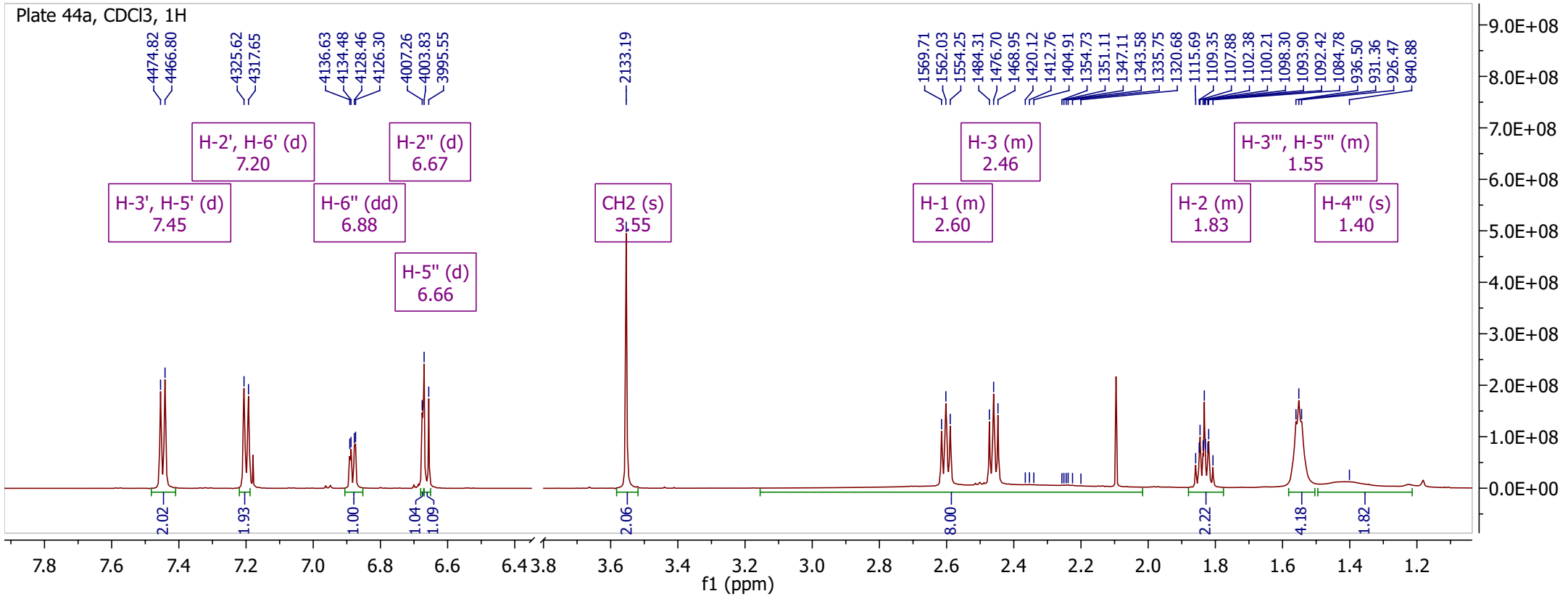
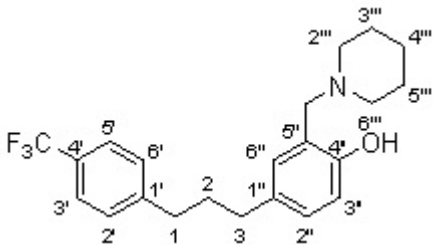


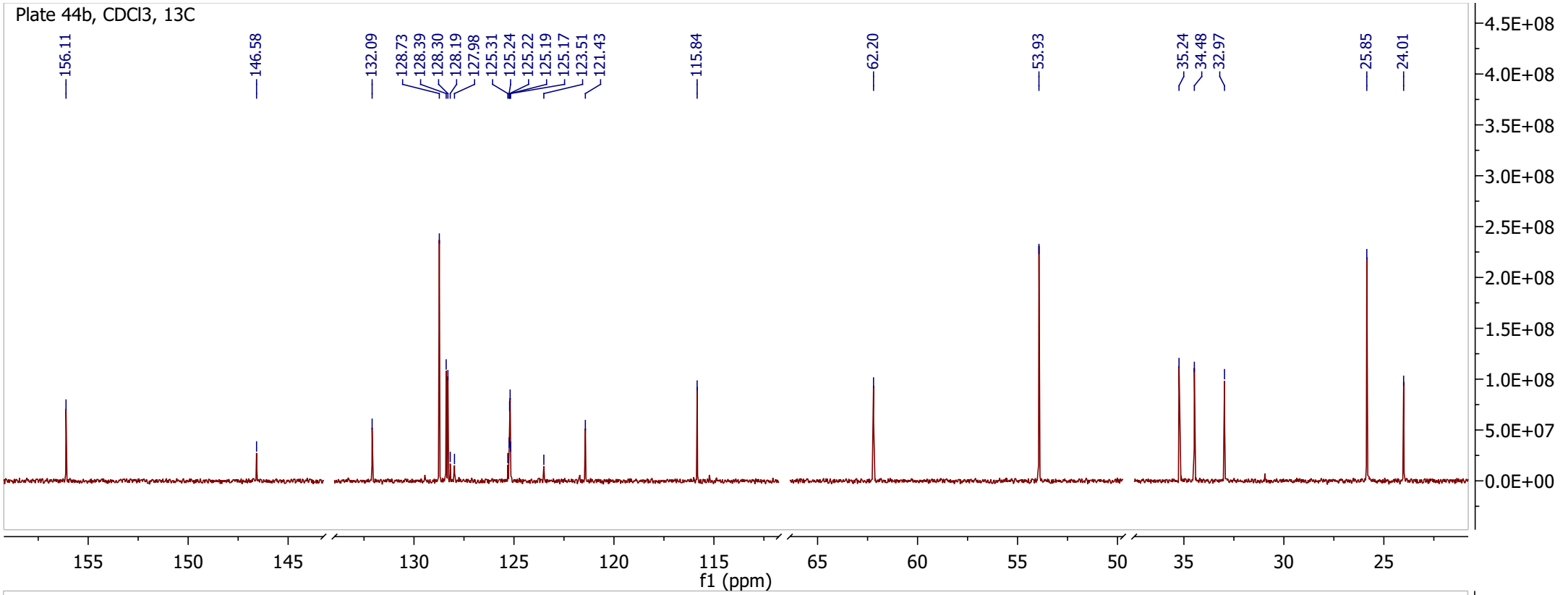
Plate 44a, CDCl3, 1H
4474.82
4466.80
4325.62
4317.65
4136.63
4134.48
4128.46
4126.30
4007.26
4003.83
3995.55
2133.19
1569.71
1562.03
1554.25
1484.31
1476.70
1468.95
1420.12
1412.76
1404.91
1354.73
1351.11
1347.11
1343.58
1335.75
1320.68
1115.69
1109.35
1107.88
1102.38
1100.21
1098.30
1093.90
1092.42
1084.78
936.50
931.36
926.47
840.88
H-2', H-6' (d)
7.20
H-2" (d)
6.67
H-3 (m)
2.46
H-3"', H-5"' (m)
1.55
H-3', H-5' (d)
7.45
H-6" (dd)
6.88
CH2 (s)
3.55
H-1 (m)
2.60
H-2 (m)
1.83
H-4"' (s)
1.40
H-5" (d)
6.66
2.02
1.93
1.00
1.04
1.09
2.06
8.00
2.22
4.18
1.82
9.0E+08
8.0E+08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
f1 (ppm)

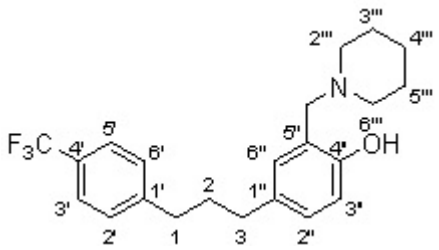

3'''
2'''
4'''
N
5'''
6'''
OH
F3C
5'
4'
6'
6''
5'
4''
1'
2
1''
3'
3''
2'
1
3
2'

66

9.0E+08
8.0E+08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

Plate 44b, CDCl3, 13C





66

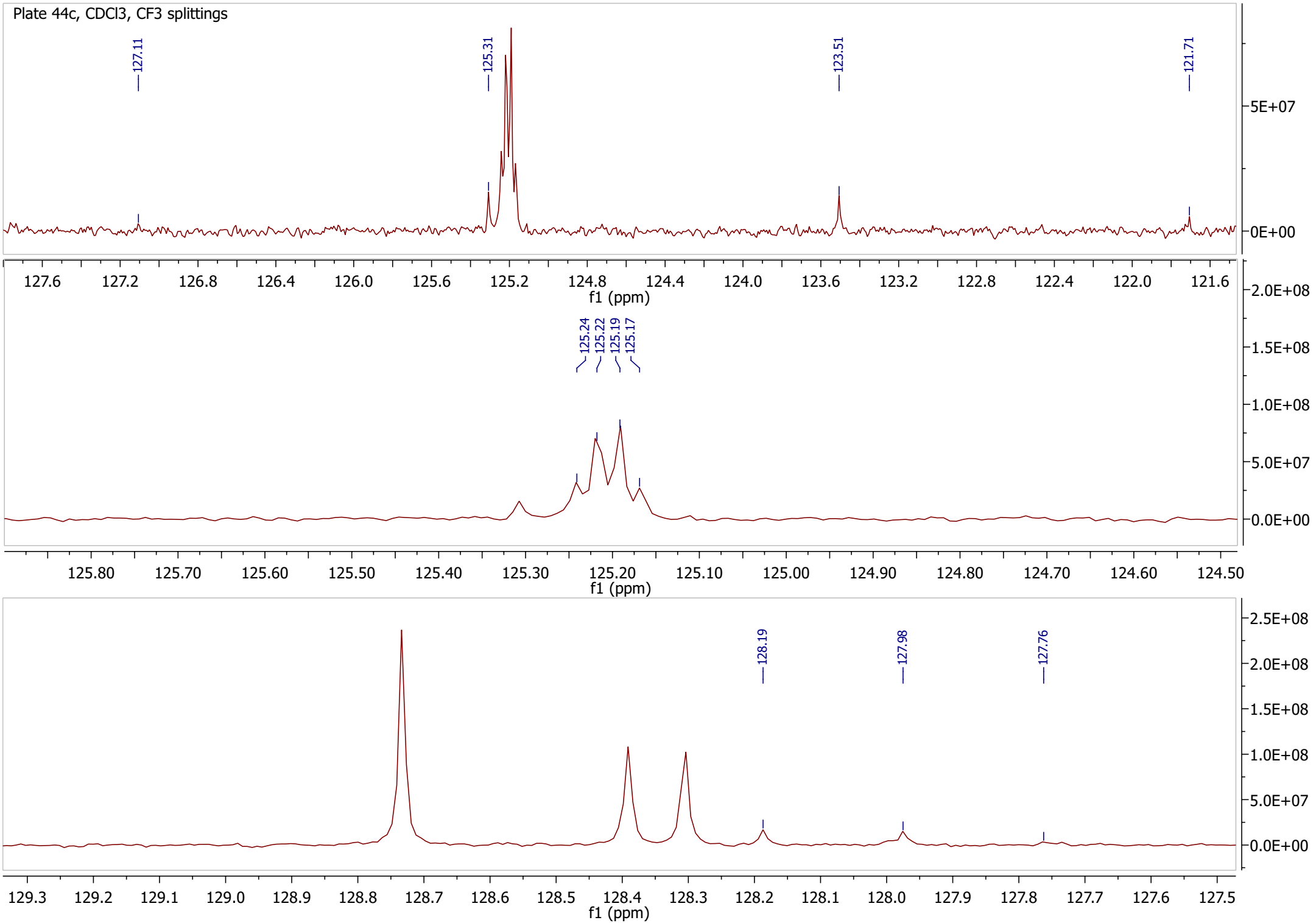
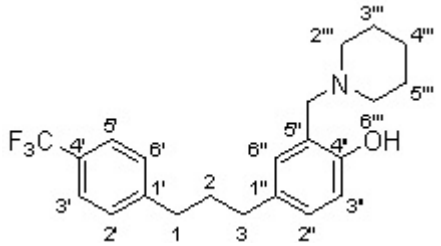


Plate 44c, CDCl3, CF3 splittings
127.11
125.31
123.51
121.71
5E+07
0E+00
127.6
127.2
126.8
126.4
126.0
125.6
125.2
124.8
124.4
124.0
123.6
123.2
122.8
122.4
122.0
121.6
f1 (ppm)
125.24
125.22
125.19
125.17
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
125.80
125.70
125.60
125.50
125.40
125.30
125.20
125.10
125.00
124.90
124.80
124.70
124.60
124.50
f1 (ppm)
128.19
127.98
127.76
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
129.3
129.2
129.1
129.0
128.9
128.8
128.7
128.6
128.5
128.4
128.3
128.2
128.1
128.0
127.9
127.8
127.7
127.6
127.5
f1 (ppm)

Plate 44d, CDCl3, 19F



66

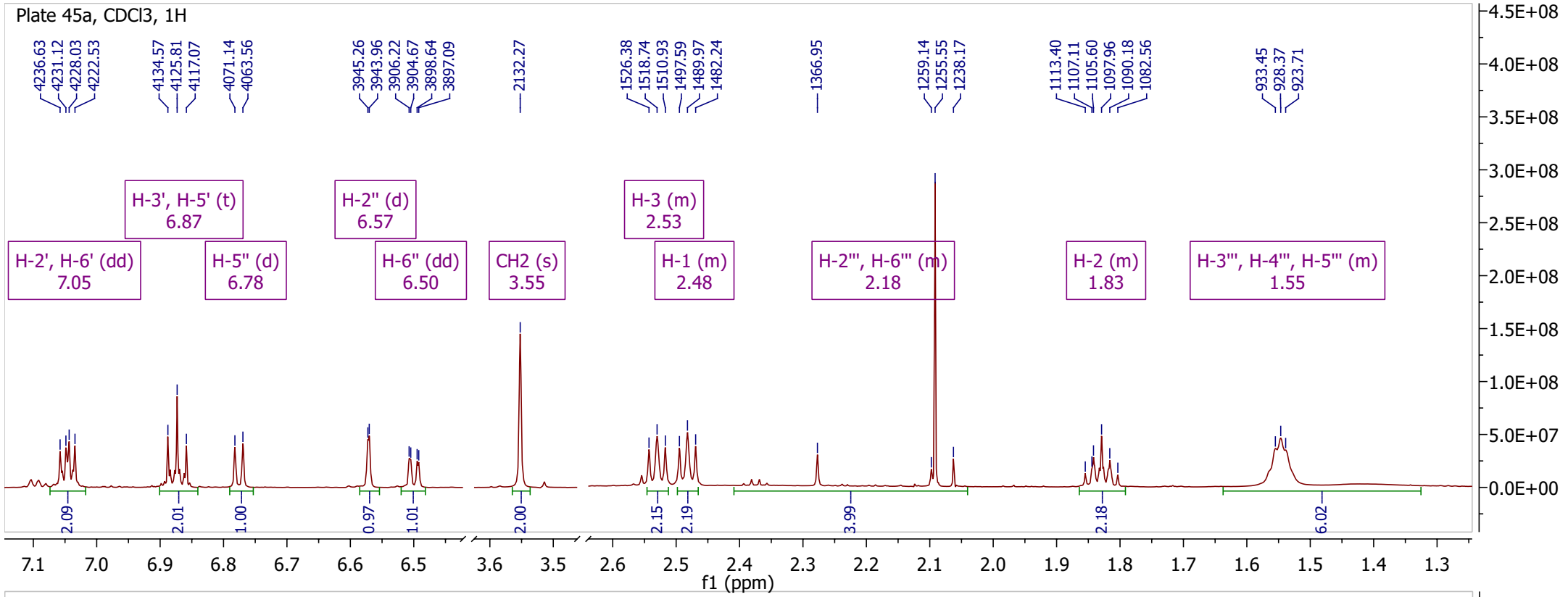
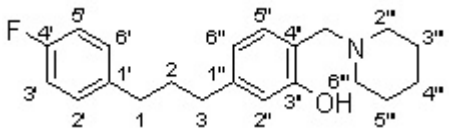


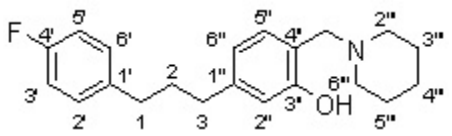
Plate 45a, CDCl3, 1H
4236.63
4231.12
4228.03
4222.53
4134.57
4125.81
4117.07
4071.14
4063.56
3945.26
3943.96
3906.22
3904.67
3898.64
3897.09
2132.27
1526.38
1518.74
1510.93
1497.59
1489.97
1482.24
1366.95
1259.14
1255.55
1238.17
1113.40
1107.11
1105.60
1097.96
1090.18
1082.56
933.45
928.37
923.71
H-3', H-5' (t)
6.87
H-2" (d)
6.57
H-3 (m)
2.53
H-2', H-6' (dd)
7.05
H-5" (d)
6.78
H-6" (dd)
6.50
CH2 (s)
3.55
H-1 (m)
2.48
H-2‴, H-6‴ (m)
2.18
H-2 (m)
1.83
H-3‴, H-4‴, H-5‴ (m)
1.55
2.09
2.01
1.00
0.97
1.01
2.00
2.15
2.19
3.99
2.18
6.02
f1 (ppm)


F
4'
5'
6'
1'
2
3'
2'
1
3
6"
5'
4'
1"
2'
3"
OH
N
2"
3"
6"
4"
5"

67

1.00
f1 (ppm)

Plate 45b, CDCl3, 13C APT



67

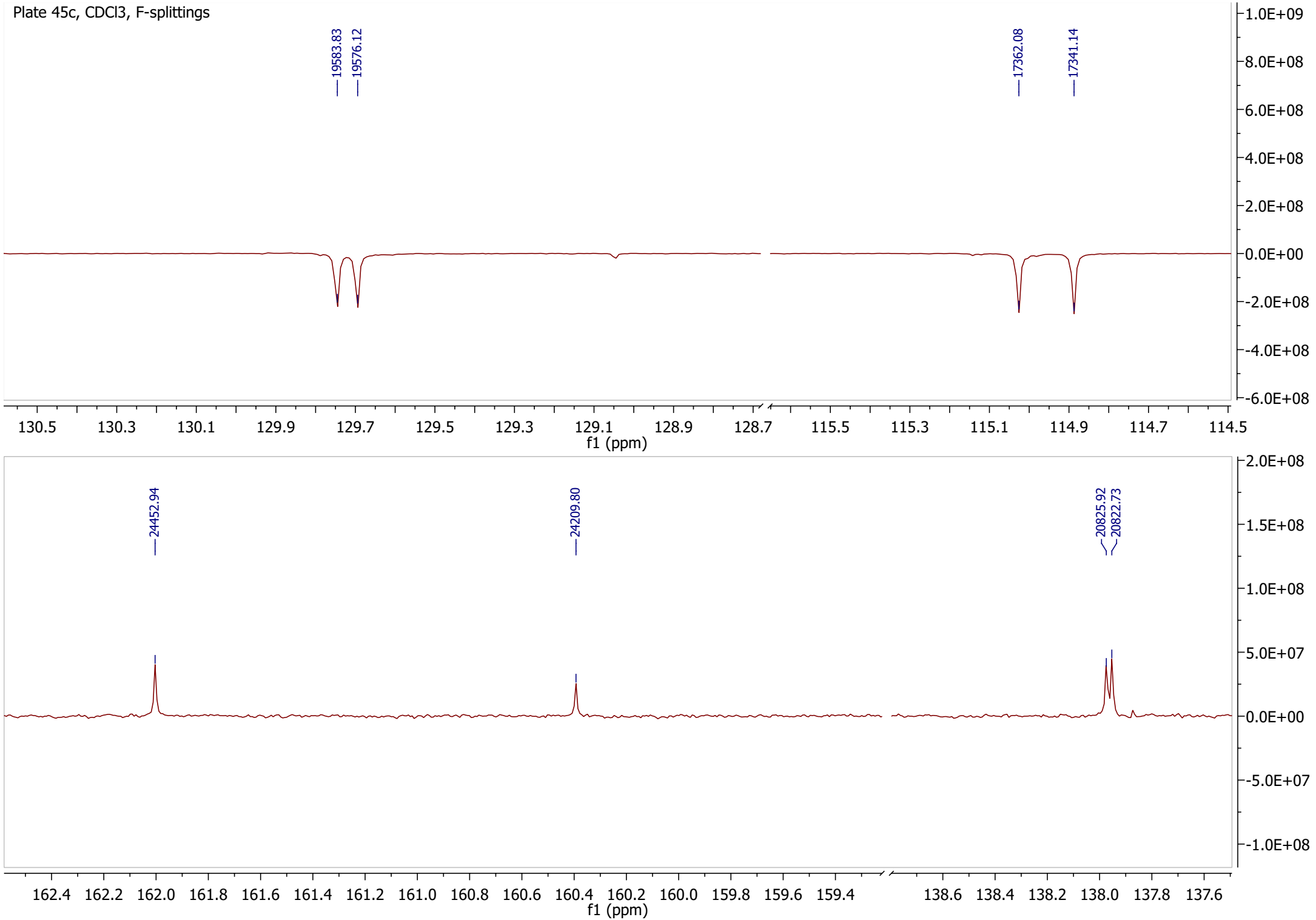
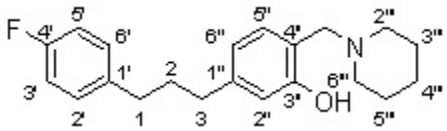


Plate 45c, CDCl3, F-splittings
19583.83
19576.12
17362.08
17341.14
1.0E+09
8.0E+08
6.0E+08
4.0E+08
2.0E+08
0.0E+00
-2.0E+08
-4.0E+08
-6.0E+08
130.5
130.3
130.1
129.9
129.7
129.5
129.3
129.1
128.9
128.7
115.5
115.3
115.1
114.9
114.7
114.5
f1 (ppm)
24452.94
24209.80
20825.92
20822.73
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
-1.0E+08
162.4
162.2
162.0
161.8
161.6
161.4
161.2
161.0
160.8
160.6
160.4
160.2
160.0
159.8
159.6
159.4
138.6
138.4
138.2
138.0
137.8
137.6
f1 (ppm)

Plate 45d, CDCl3, 19F



67

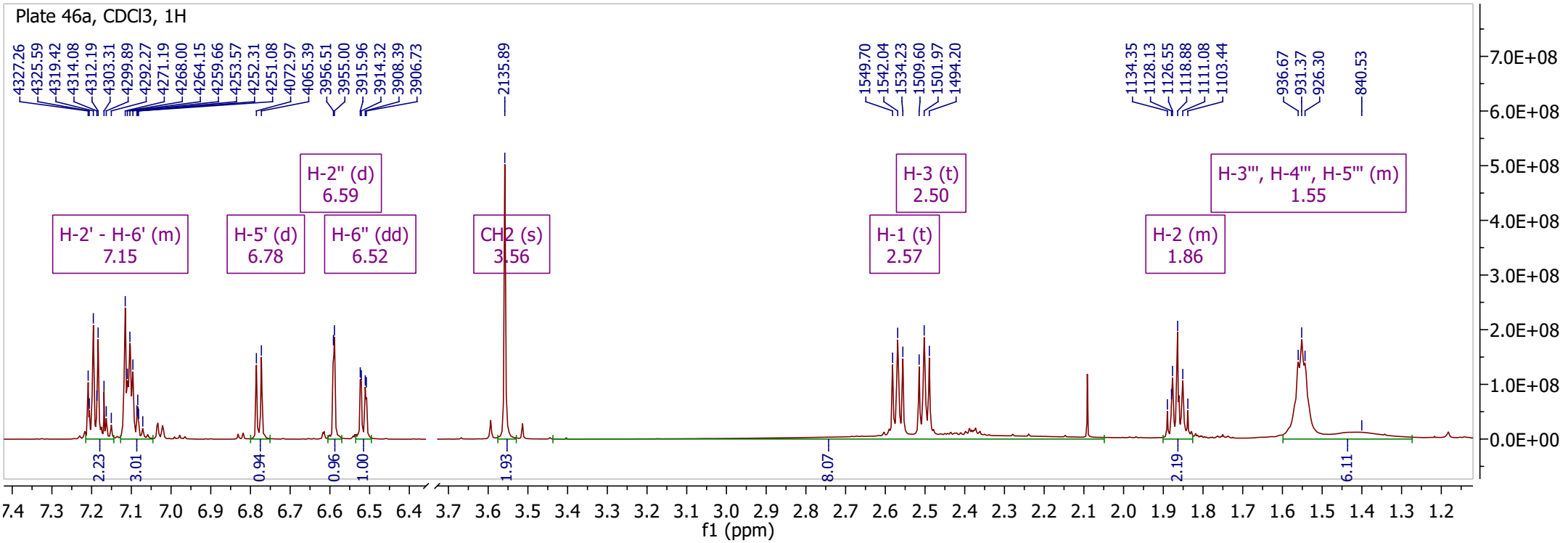
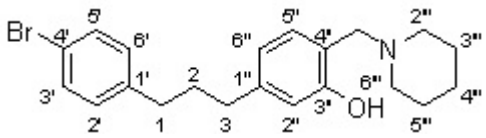


Plate 46a, CDCl3, 1H
4327.26
4325.59
4319.42
4314.08
4312.19
4303.31
4299.89
4292.27
4271.19
4268.00
4264.15
4259.66
4253.57
4252.31
4251.08
4072.97
4065.39
3956.51
3955.00
3915.96
3914.32
3908.39
3906.73
2135.89
1549.70
1542.04
1534.23
1509.60
1501.97
1494.20
1134.35
1128.13
1126.55
1118.88
1111.08
1103.44
936.67
931.37
926.30
840.53
H-2' - H-6' (m)
7.15
H-5' (d)
6.78
H-2" (d)
6.59
H-6" (dd)
6.52
CH2 (s)
3.56
H-3 (t)
2.50
H-1 (t)
2.57
H-2 (m)
1.86
H-3"', H-4"', H-5"' (m)
1.55
2.23
3.01
0.94
0.96
1.00
1.93
8.07
2.19
6.11
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
f1 (ppm)


Br
OH
N

118

5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

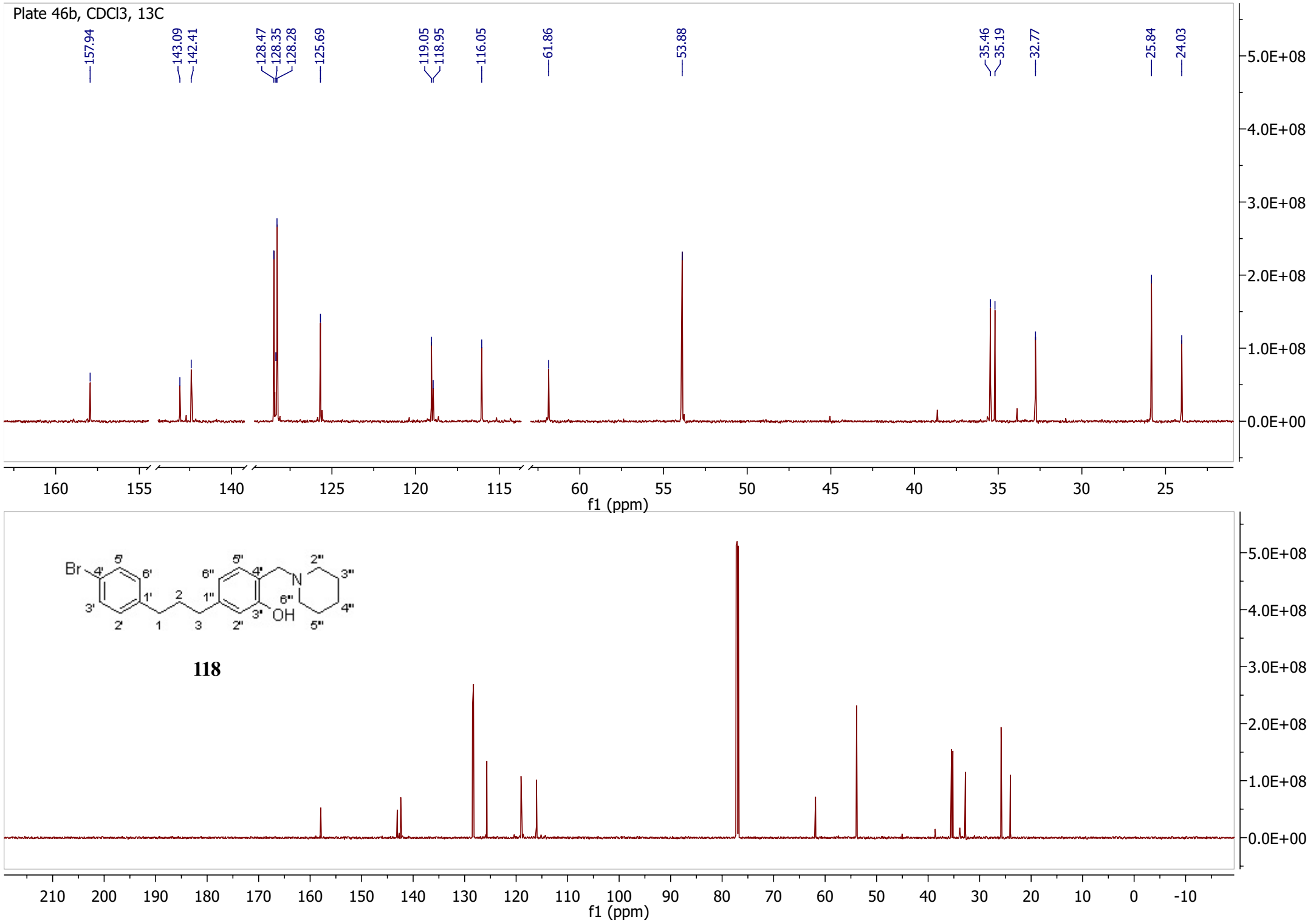


Plate 46b, CDCl3, 13C
157.94
143.09
142.41
128.47
128.35
128.28
125.69
119.05
118.95
116.05
61.86
53.88
35.46
35.19
32.77
25.84
24.03
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
160
155
140
125
120
115
60
55
50
45
40
35
30
25
f1 (ppm)
Br
OH
N
118
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

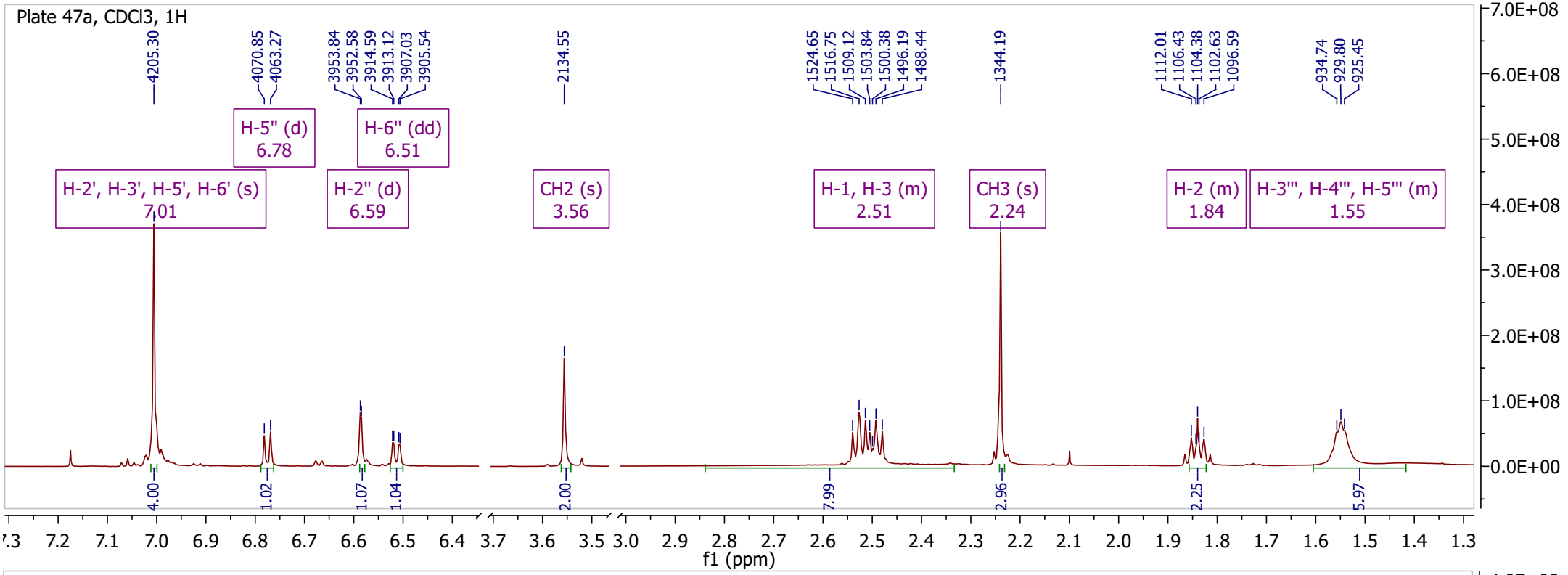
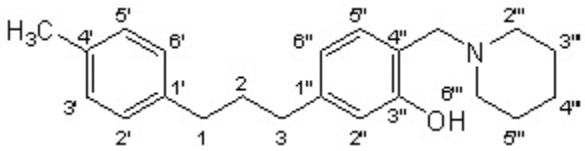


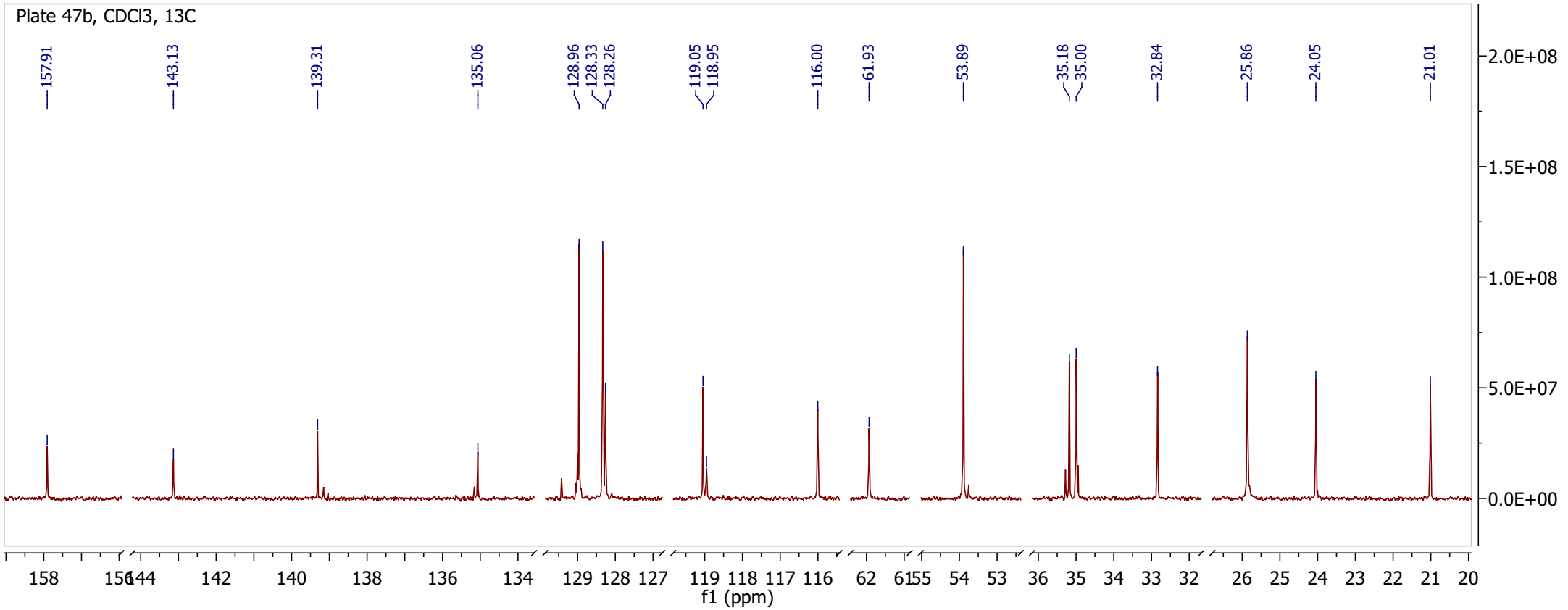
Plate 47a, CDCl3, 1H
4205.30
4070.85
4063.27
3953.84
3952.58
3914.59
3913.12
3907.03
3905.54
2134.55
1524.65
1516.75
1509.12
1503.84
1500.38
1496.19
1488.44
1344.19
1112.01
1106.43
1104.38
1102.63
1096.59
934.74
929.80
925.45
H-5" (d) 6.78
H-6" (dd) 6.51
H-2', H-3', H-5', H-6' (s) 7.01
H-2" (d) 6.59
CH2 (s) 3.56
H-1, H-3 (m) 2.51
CH3 (s) 2.24
H-2 (m) 1.84
H-3"', H-4"', H-5"' (m) 1.55
4.00
1.02
1.07
1.04
2.00
7.99
2.96
2.25
5.97
f1 (ppm)

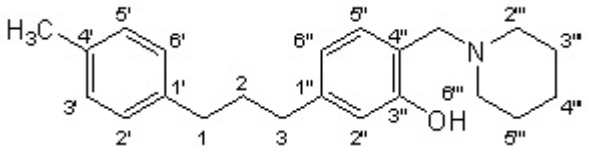

H3C
OH
N

68

f1 (ppm)

Plate 47b, CDCl3, 13C





68

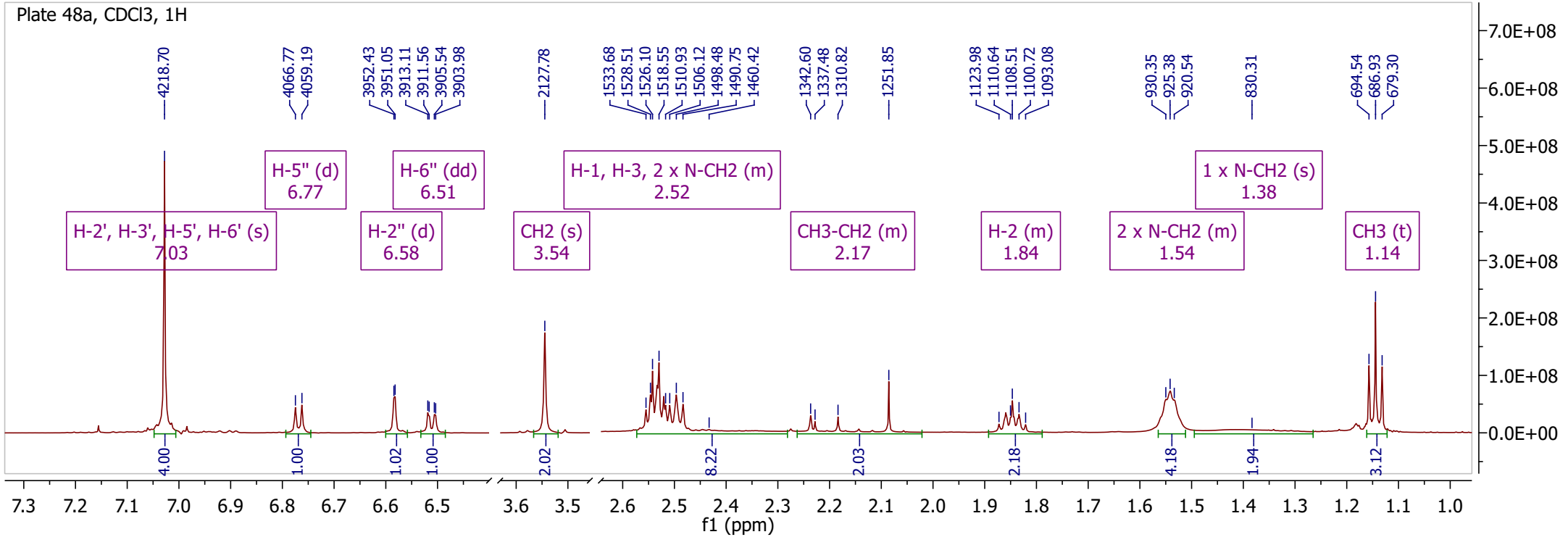
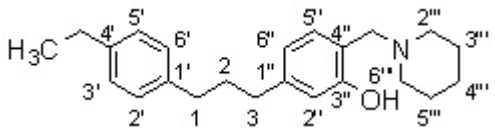


Plate 48a, CDCl3, 1H
4218.70
4066.77
4059.19
3952.43
3951.05
3913.11
3911.56
3905.54
3903.98
2127.78
1533.68
1528.51
1526.10
1518.55
1510.93
1506.12
1498.48
1490.75
1460.42
1342.60
1337.48
1310.82
1251.85
1123.98
1110.64
1108.51
1100.72
1093.08
930.35
925.38
920.54
830.31
694.54
686.93
679.30
H-2', H-3', H-5', H-6' (s)
7.03
H-5" (d)
6.77
H-6" (dd)
6.51
H-2" (d)
6.58
CH2 (s)
3.54
H-1, H-3, 2 x N-CH2 (m)
2.52
CH3-CH2 (m)
2.17
H-2 (m)
1.84
2 x N-CH2 (m)
1.54
1 x N-CH2 (s)
1.38
CH3 (t)
1.14
4.00
1.00
1.02
1.00
2.02
8.22
2.03
2.18
4.18
1.94
3.12
f1 (ppm)


H3C
OH
N

69

f1 (ppm)

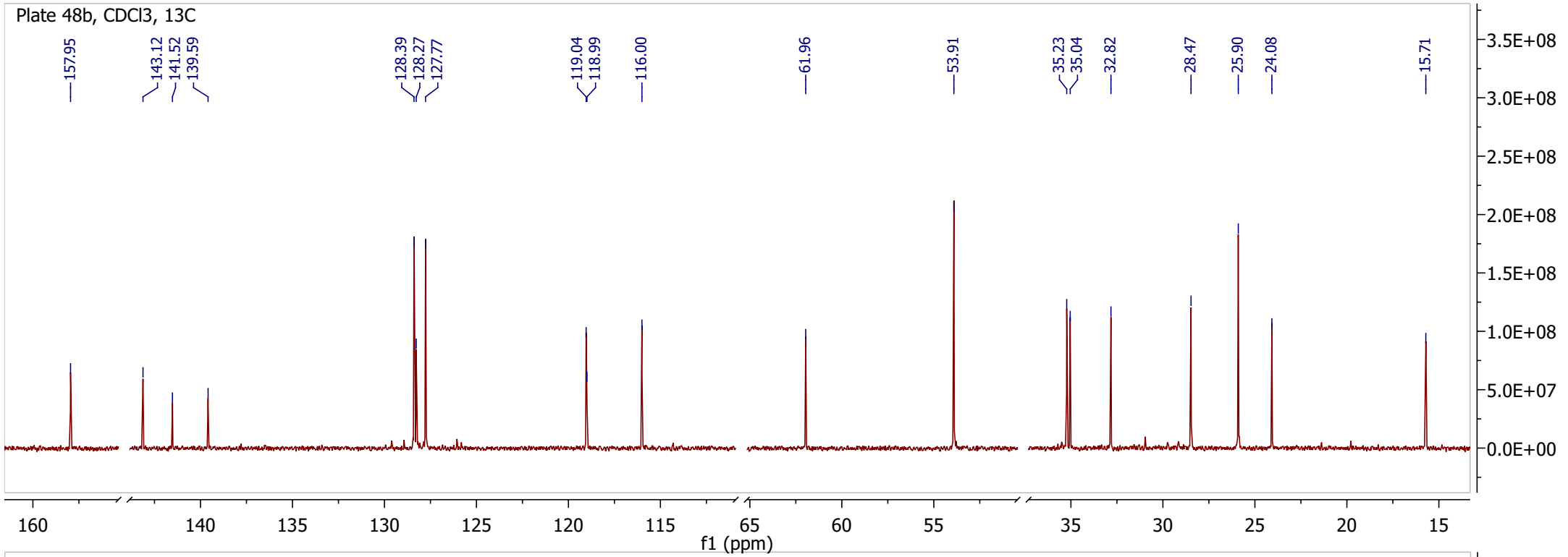
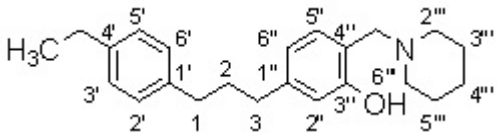


Plate 48b, CDCl3, 13C
157.95
143.12
141.52
139.59
128.39
128.27
127.77
119.04
118.99
116.00
61.96
53.91
35.23
35.04
32.82
28.47
25.90
24.08
15.71
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
160
140
135
130
125
120
115
65
60
55
35
30
25
20
15
f1 (ppm)


H3C
OH
N

69

3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

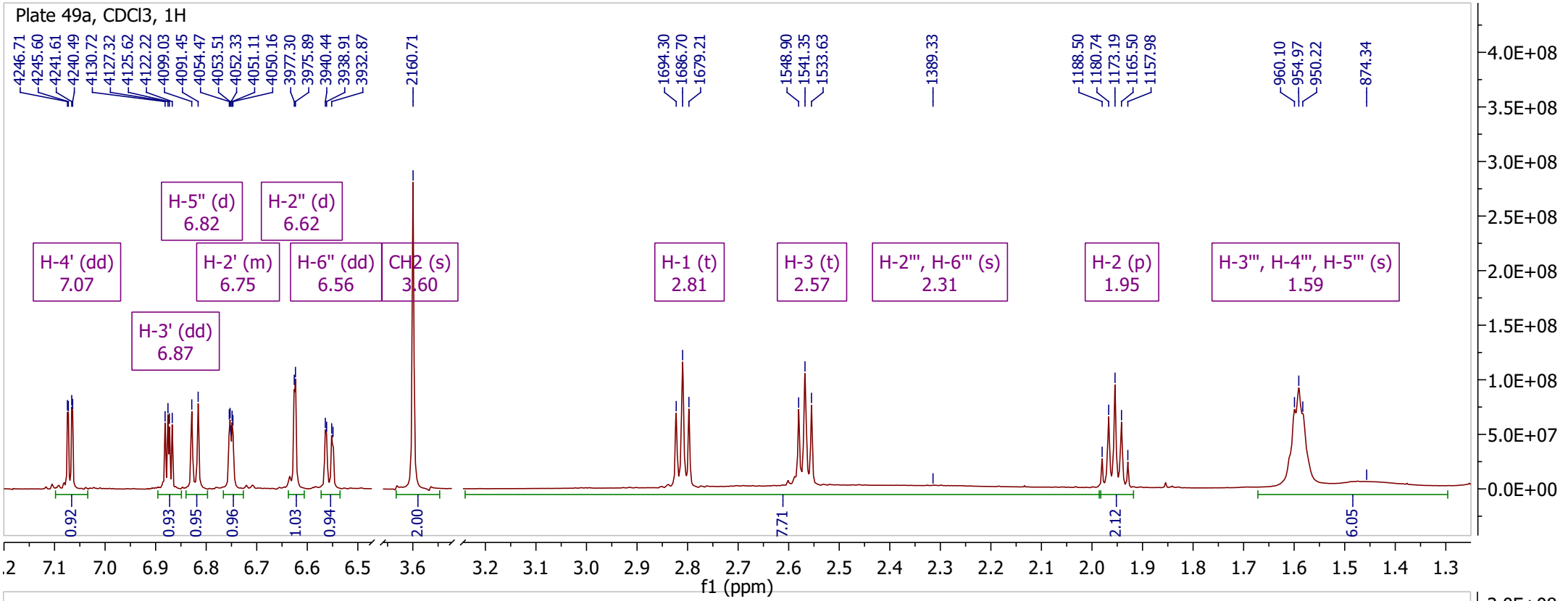
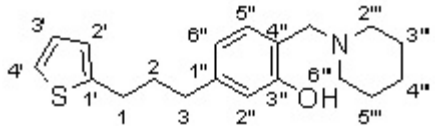


Plate 49a, CDCl3, 1H
4246.71
4245.60
4241.61
4240.49
4130.72
4127.32
4125.62
4122.22
4099.03
4091.45
4054.47
4053.51
4052.33
4051.11
4050.16
3977.30
3975.89
3940.44
3938.91
3932.87
2160.71
1694.30
1686.70
1679.21
1548.90
1541.35
1533.63
1389.33
1188.50
1180.74
1173.19
1165.50
1157.98
960.10
954.97
950.22
874.34
H-5" (d) 6.82
H-2" (d) 6.62
H-4' (dd) 7.07
H-2' (m) 6.75
H-6" (dd) 6.56
CH2 (s) 3.60
H-1 (t) 2.81
H-3 (t) 2.57
H-2‴, H-6‴ (s) 2.31
H-2 (p) 1.95
H-3‴, H-4‴, H-5‴ (s) 1.59
H-3' (dd) 6.87
0.92
0.93
0.95
0.96
1.03
0.94
2.00
7.71
2.12
6.05
f1 (ppm)


3'
2'
4'
S
1'
2
1
3
5"
6"
4"
1"
3"
2"
N
2‴
3"
6"
OH
4"
5‴

70

f1 (ppm)

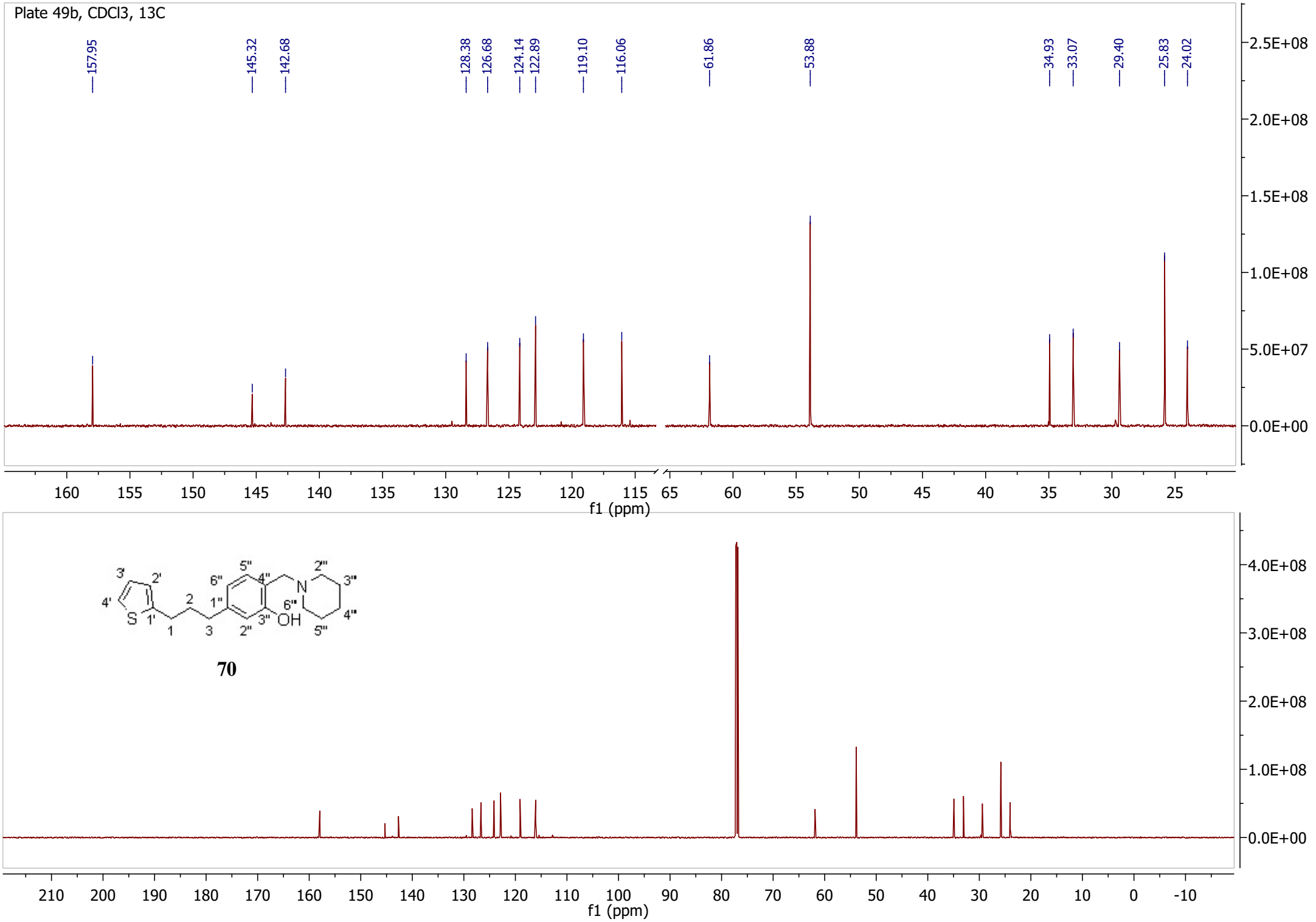


Plate 49b, CDCl3, 13C
157.95
145.32
142.68
128.38
126.68
124.14
122.89
119.10
116.06
61.86
53.88
34.93
33.07
29.40
25.83
24.02
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
160 155 150 145 140 135 130 125 120 115 65 60 55 50 45 40 35 30 25
f1 (ppm)
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

70

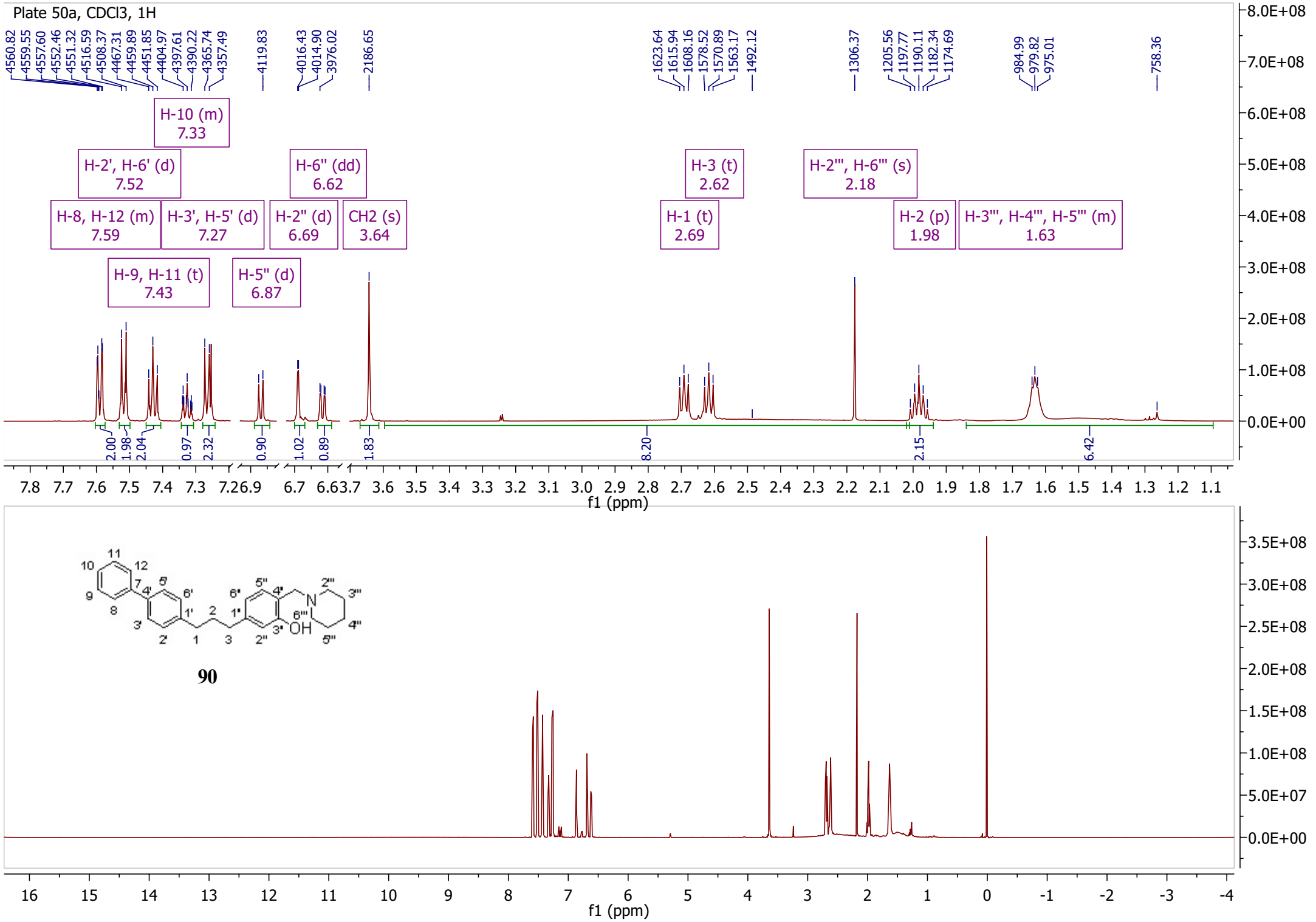


Plate 50a, CDCl3, 1H
4560.82
4559.55
4557.60
4552.46
4551.32
4516.59
4508.37
4467.31
4459.89
4451.85
4404.97
4397.61
4390.22
4365.74
4357.49
4119.83
4016.43
4014.90
3976.02
2186.65
1623.64
1615.94
1608.16
1578.52
1570.89
1563.17
1492.12
1306.37
1205.56
1197.77
1190.11
1182.34
1174.69
984.99
979.82
975.01
758.36
H-10 (m)
7.33
H-2', H-6' (d)
7.52
H-6" (dd)
6.62
H-3 (t)
2.62
H-2''', H-6''' (s)
2.18
H-8, H-12 (m)
7.59
H-3', H-5' (d)
7.27
H-2" (d)
6.69
CH2 (s)
3.64
H-1 (t)
2.69
H-2 (p)
1.98
H-3''', H-4''', H-5''' (m)
1.63
H-9, H-11 (t)
7.43
H-5" (d)
6.87
2.00
1.98
2.04
0.97
2.32
0.90
1.02
0.89
1.83
8.20
2.15
6.42
f1 (ppm)
90
f1 (ppm)

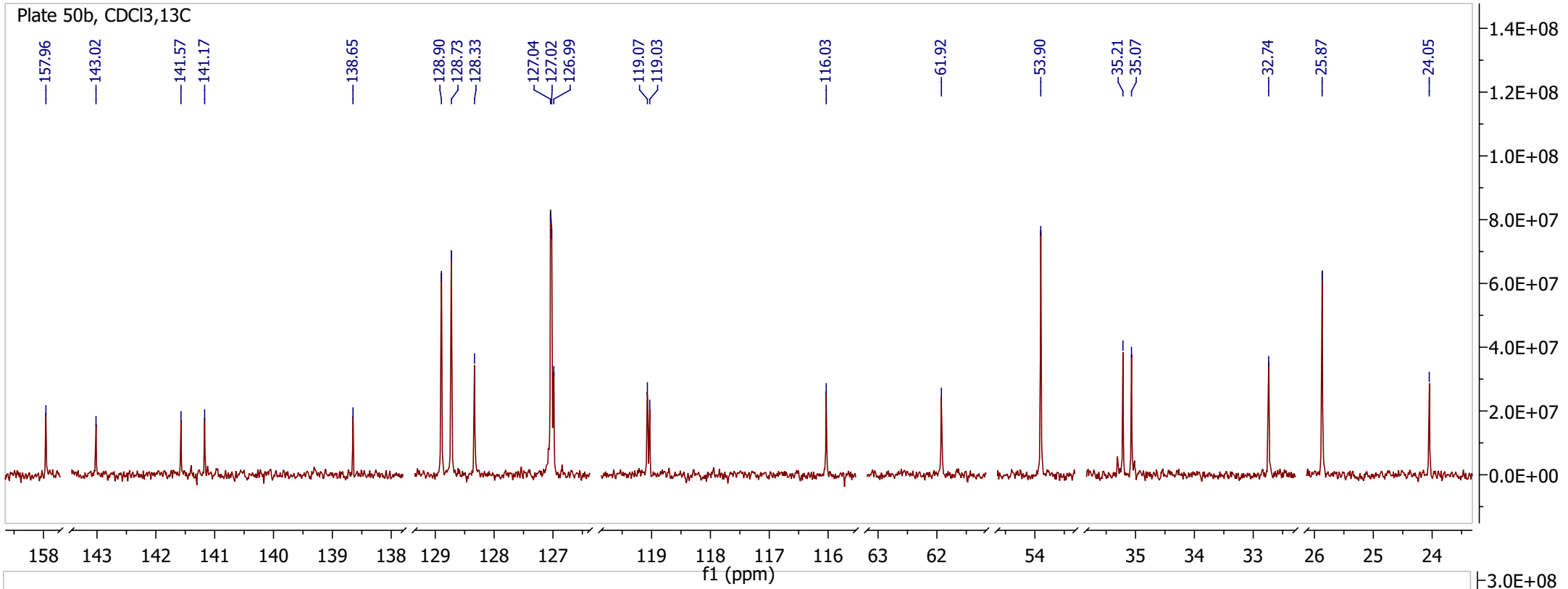
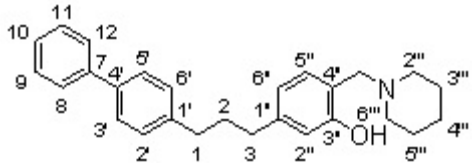


Plate 50b, CDCl3,13C
157.96
143.02
141.57
141.17
138.65
128.90
128.73
128.33
127.04
127.02
126.99
119.07
119.03
116.03
61.92
53.90
35.21
35.07
32.74
25.87
24.05
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
158 143 142 141 140 139 138 129 128 127 119 118 117 116 63 62 54 35 34 33 26 25 24
f1 (ppm)


11
10
12
7
5'
9
4'
6'
8
1'
2
1"
6"
5"
4'
2'''
3'''
N
6'''
3'
3"
OH
4"
2'
1
3
2"
5'''

90

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

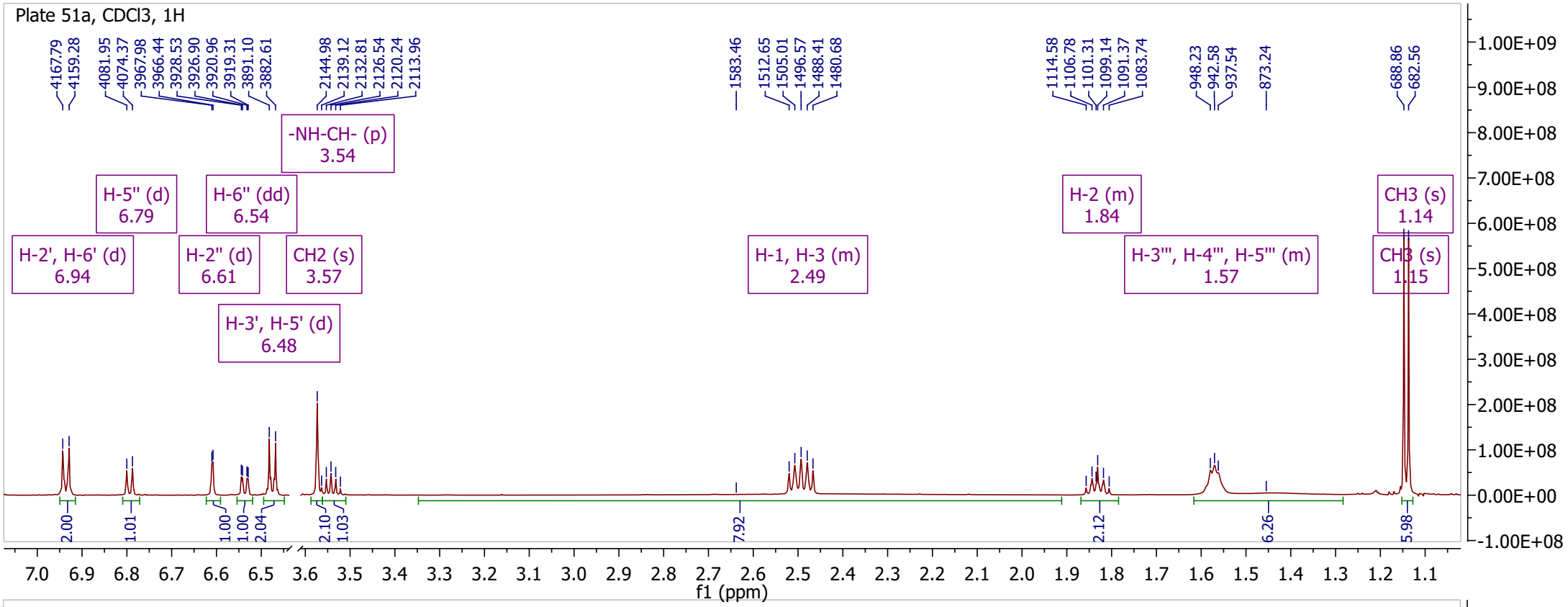
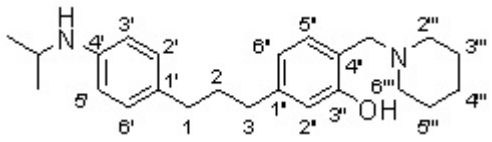


Plate 51a, CDCl3, 1H
4167.79
4159.28
4081.95
4074.37
3967.98
3966.44
3928.53
3926.90
3920.96
3919.31
3891.10
3882.61
2144.98
2139.12
2132.81
2126.54
2120.24
2113.96
1583.46
1512.65
1505.01
1496.57
1488.41
1480.68
1114.58
1106.78
1101.31
1099.14
1091.37
1083.74
948.23
942.58
937.54
873.24
688.86
682.56
-NH-CH- (p)
3.54
H-5'' (d)
6.79
H-6'' (dd)
6.54
H-2', H-6' (d)
6.94
H-2'' (d)
6.61
CH2 (s)
3.57
H-3', H-5' (d)
6.48
H-1, H-3 (m)
2.49
H-2 (m)
1.84
H-3''', H-4''', H-5''' (m)
1.57
CH3 (s)
1.14
CH3 (s)
1.15
2.00
1.01
1.00
1.00
2.04
2.10
1.03
7.92
2.12
6.26
5.98
f1 (ppm)



71

f1 (ppm)

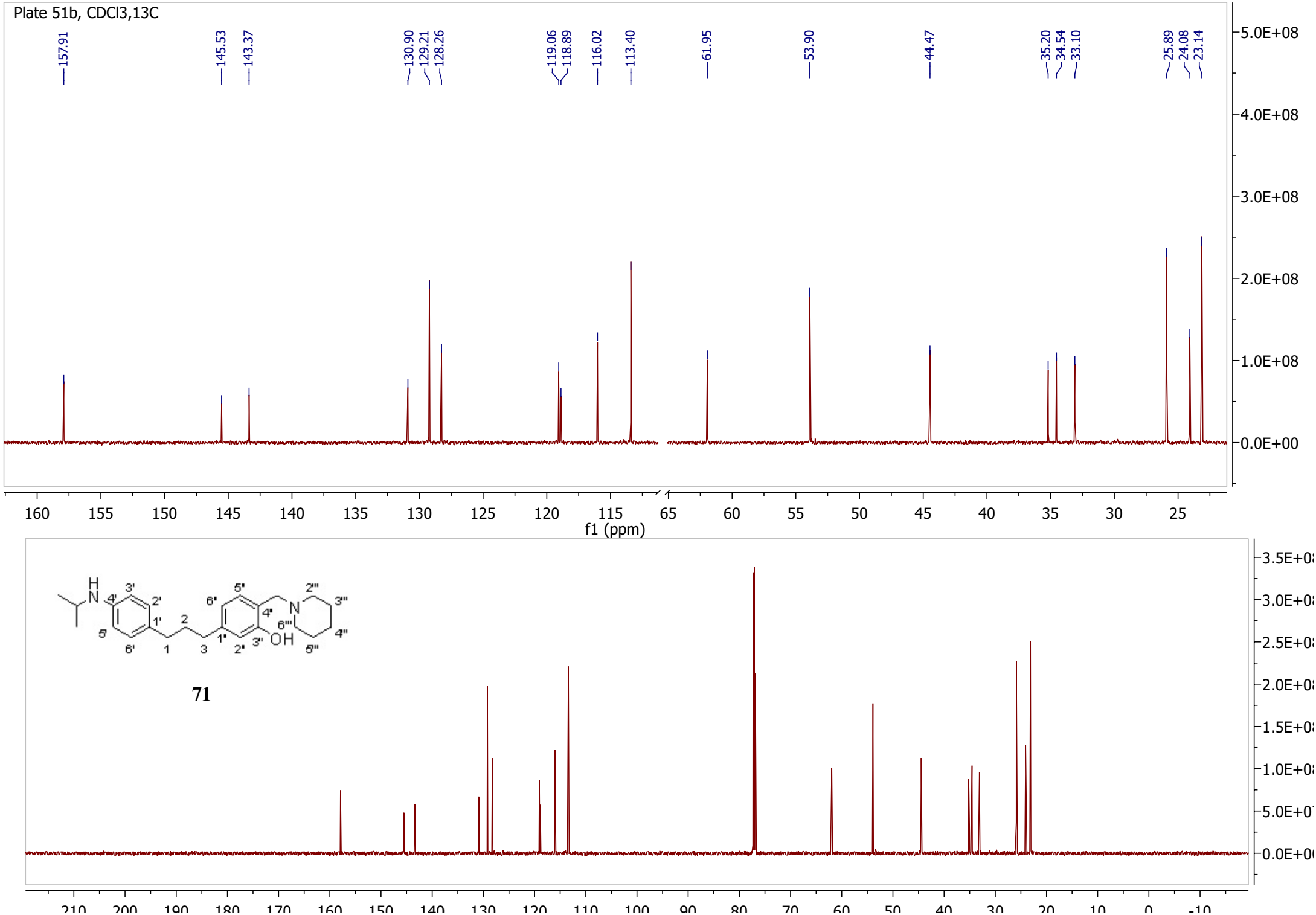


Plate 51b, CDCl3,13C
157.91
145.53
143.37
130.90
129.21
128.26
119.06
118.89
116.02
113.40
61.95
53.90
44.47
35.20
34.54
33.10
25.89
24.08
23.14
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
160 155 150 145 140 135 130 125 120 115 65 60 55 50 45 40 35 30 25
f1 (ppm)
71
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

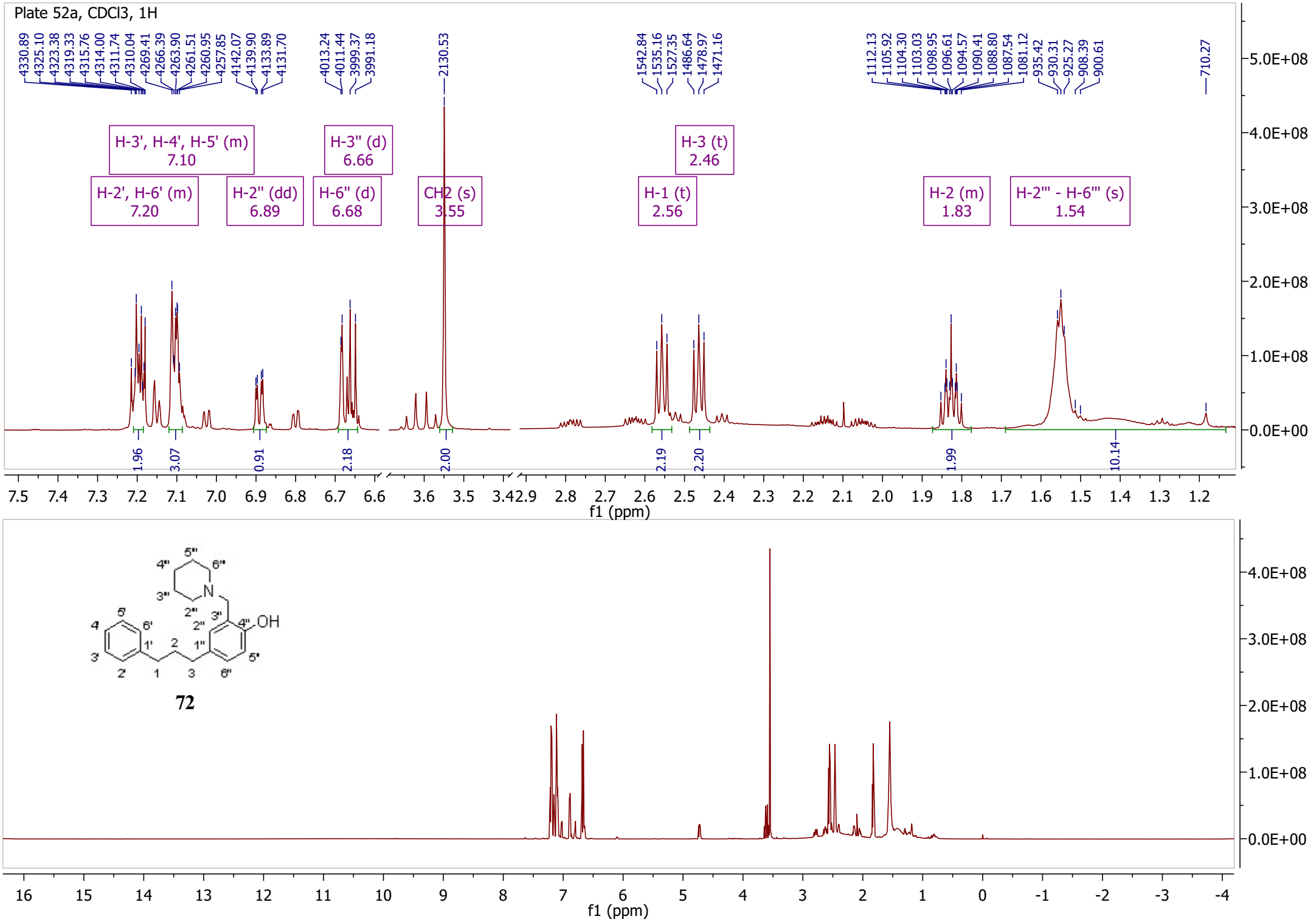


Plate 52a, CDCl3, 1H
H-3', H-4', H-5' (m) 7.10
H-2', H-6' (m) 7.20
H-2" (dd) 6.89
H-6" (d) 6.68
H-3" (d) 6.66
CH2 (s) 3.55
H-1 (t) 2.56
H-3 (t) 2.46
H-2 (m) 1.83
H-2"' - H-6"' (s) 1.54
1.96
3.07
0.91
2.18
2.00
2.19
2.20
1.99
10.14
f1 (ppm)
OH
72
f1 (ppm)

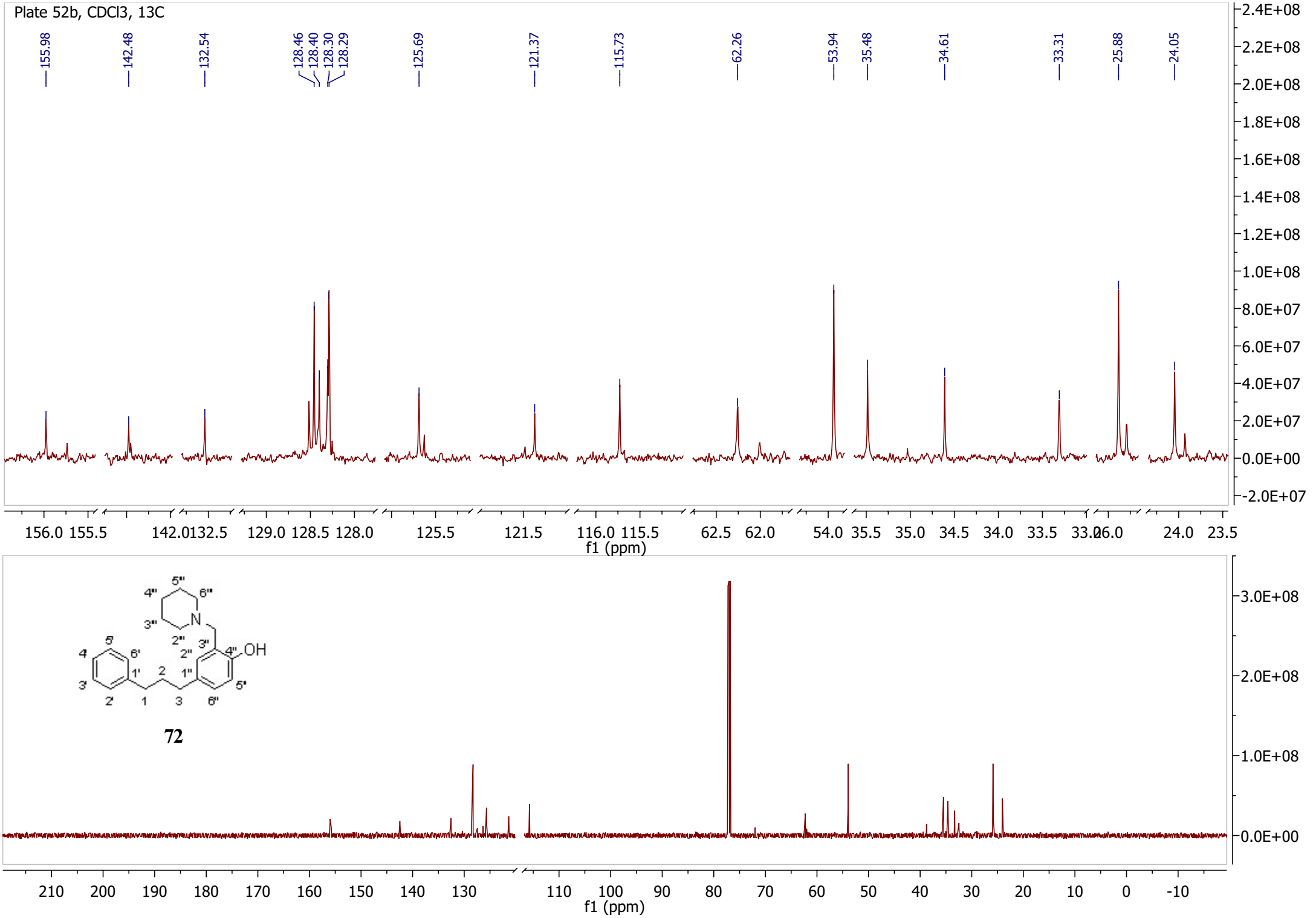


Plate 52b, CDCl3, 13C
155.98
142.48
132.54
128.46
128.40
128.30
128.29
125.69
121.37
115.73
62.26
53.94
35.48
34.61
33.31
25.88
24.05
f1 (ppm)
OH
72

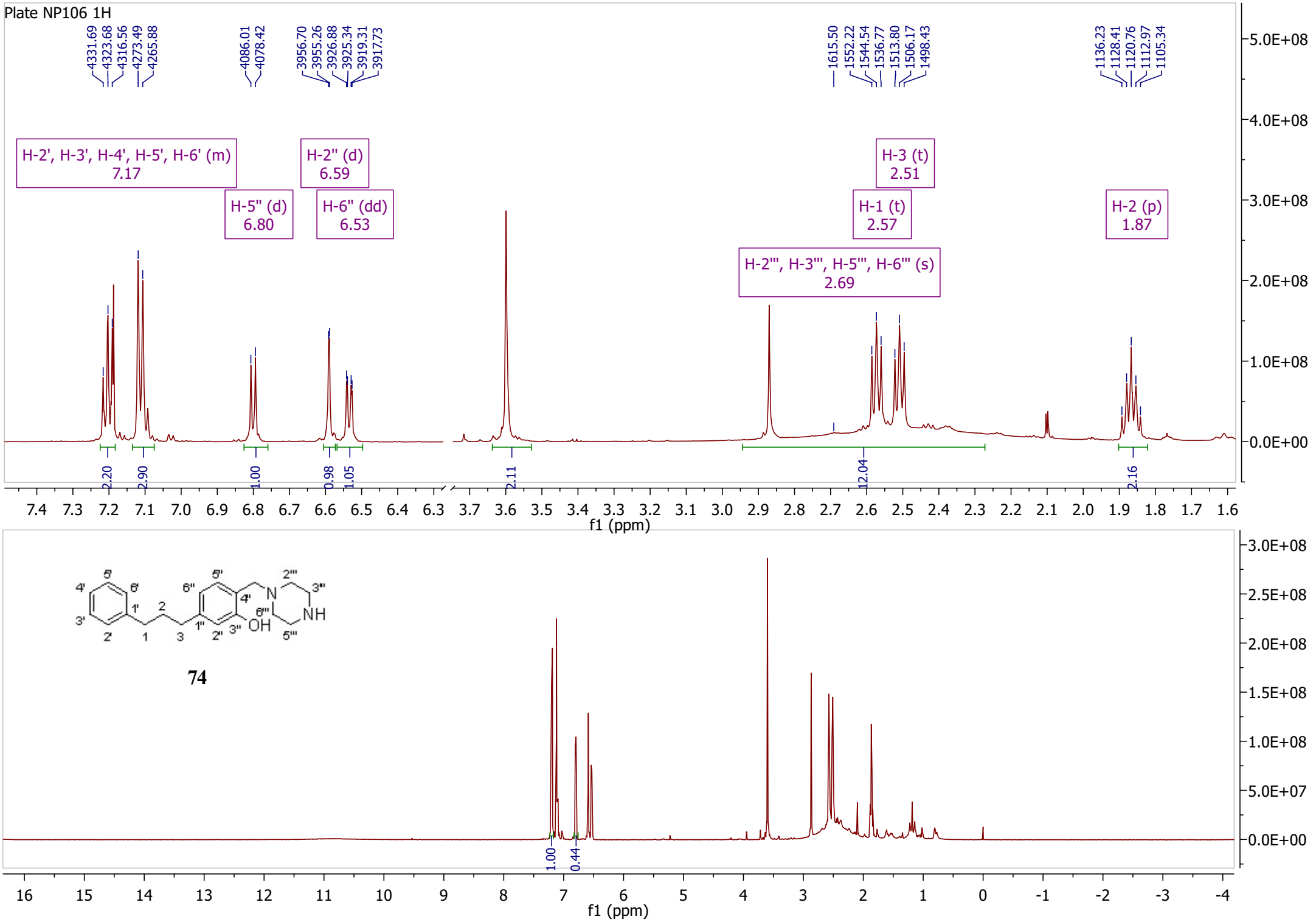


Plate NP106 1H
4331.69
4323.68
4316.56
4273.49
4265.88
4086.01
4078.42
3956.70
3955.26
3926.88
3925.34
3919.31
3917.73
1615.50
1552.22
1544.54
1536.77
1513.80
1506.17
1498.43
1136.23
1128.41
1120.76
1112.97
1105.34
H-2', H-3', H-4', H-5', H-6' (m)
7.17
H-5" (d)
6.80
H-2" (d)
6.59
H-6" (dd)
6.53
H-2‴, H-3‴, H-5‴, H-6‴ (s)
2.69
H-1 (t)
2.57
H-3 (t)
2.51
H-2 (p)
1.87
2.20
2.90
1.00
0.98
1.05
2.11
12.04
2.16
f1 (ppm)
74
1.00
0.44
f1 (ppm)

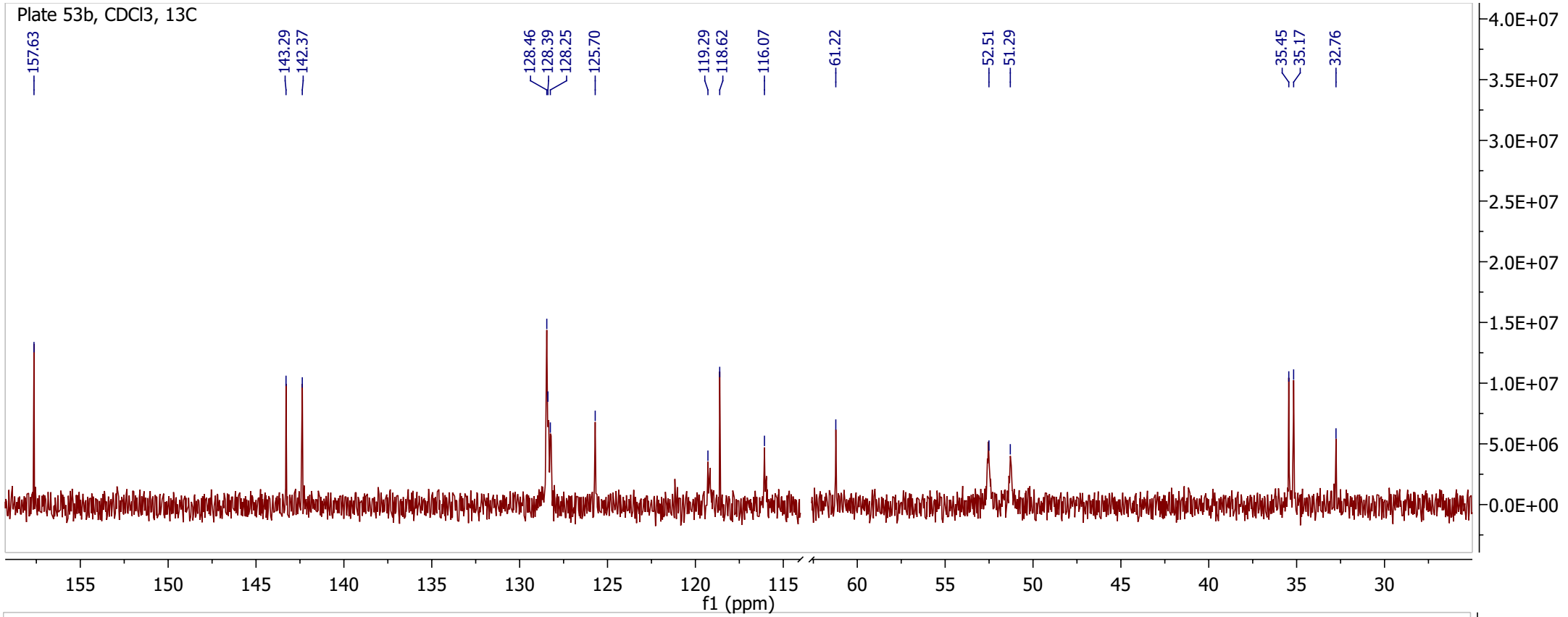
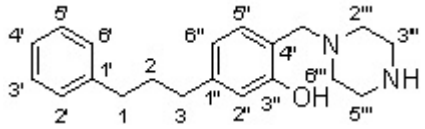


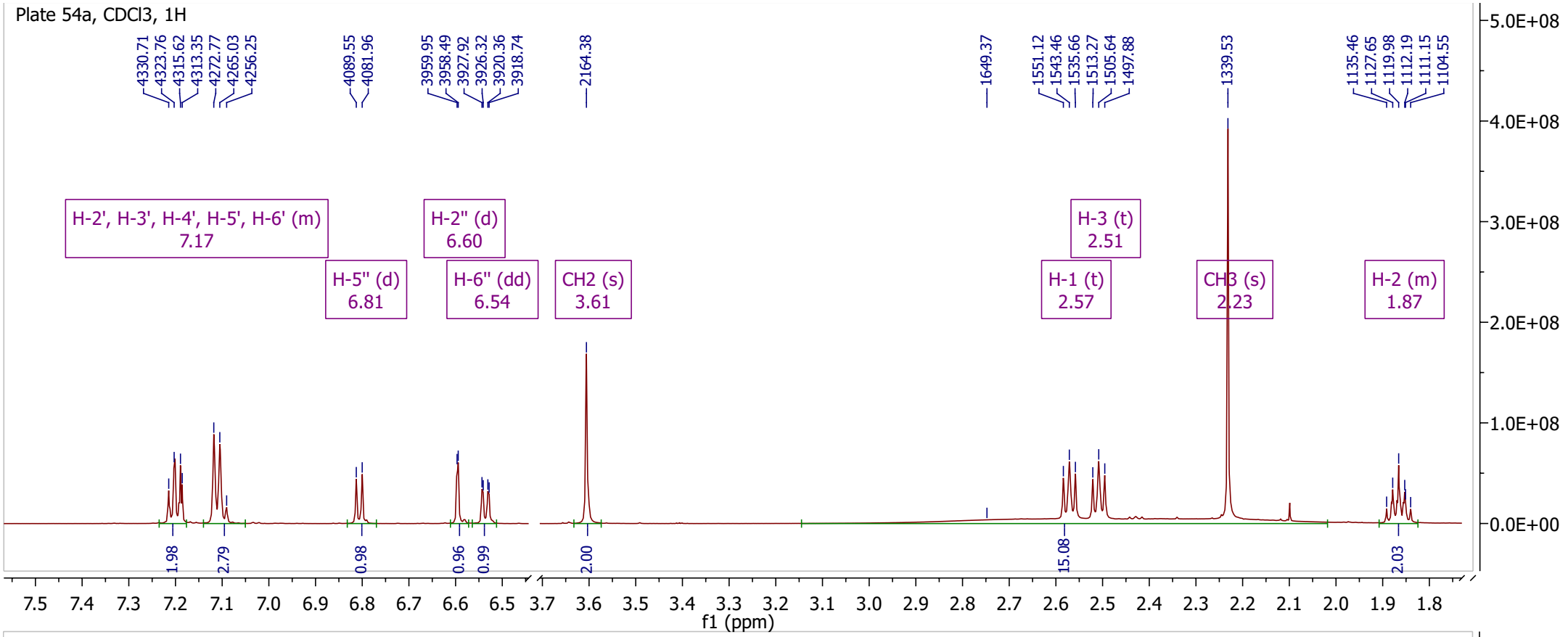
Plate 53b, CDCl3, 13C
157.63
143.29
142.37
128.46
128.39
128.25
125.70
119.29
118.62
116.07
61.22
52.51
51.29
35.45
35.17
32.76
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
155 150 145 140 135 130 125 120 115 60 55 50 45 40 35 30
f1 (ppm)

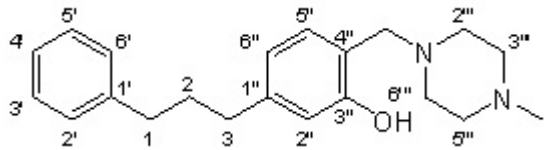

5'
4'
6'
3'
1'
2
2'
1
3
6"
5'
4'
1"
2"
3"
OH
2'''
3"
N
6'''
NH
5'''

74

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Plate 54a, CDCl3, 1H





75

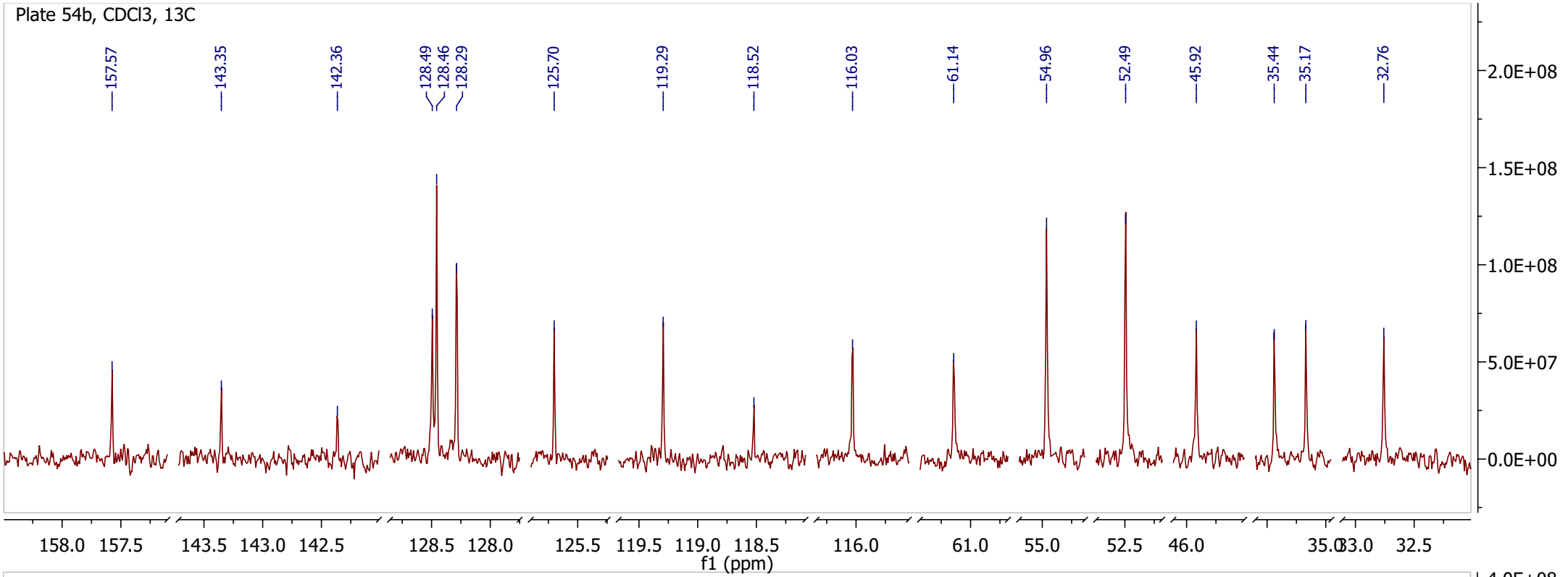
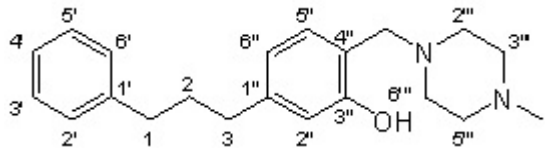


Plate 54b, CDCl3, 13C
157.57
143.35
142.36
128.49
128.46
128.29
125.70
119.29
118.52
116.03
61.14
54.96
52.49
45.92
35.44
35.17
32.76
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
158.0 157.5 143.5 143.0 142.5 128.5 128.0 125.5 119.5 119.0 118.5 116.0 61.0 55.0 52.5 46.0 35.0 33.0 32.5
f1 (ppm)


5'
6'
4'
1'
2
3'
2'
1
3
1"
6"
5'
4"
3"
2'
OH
N
2"
3"
6"
N
5"

75

4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

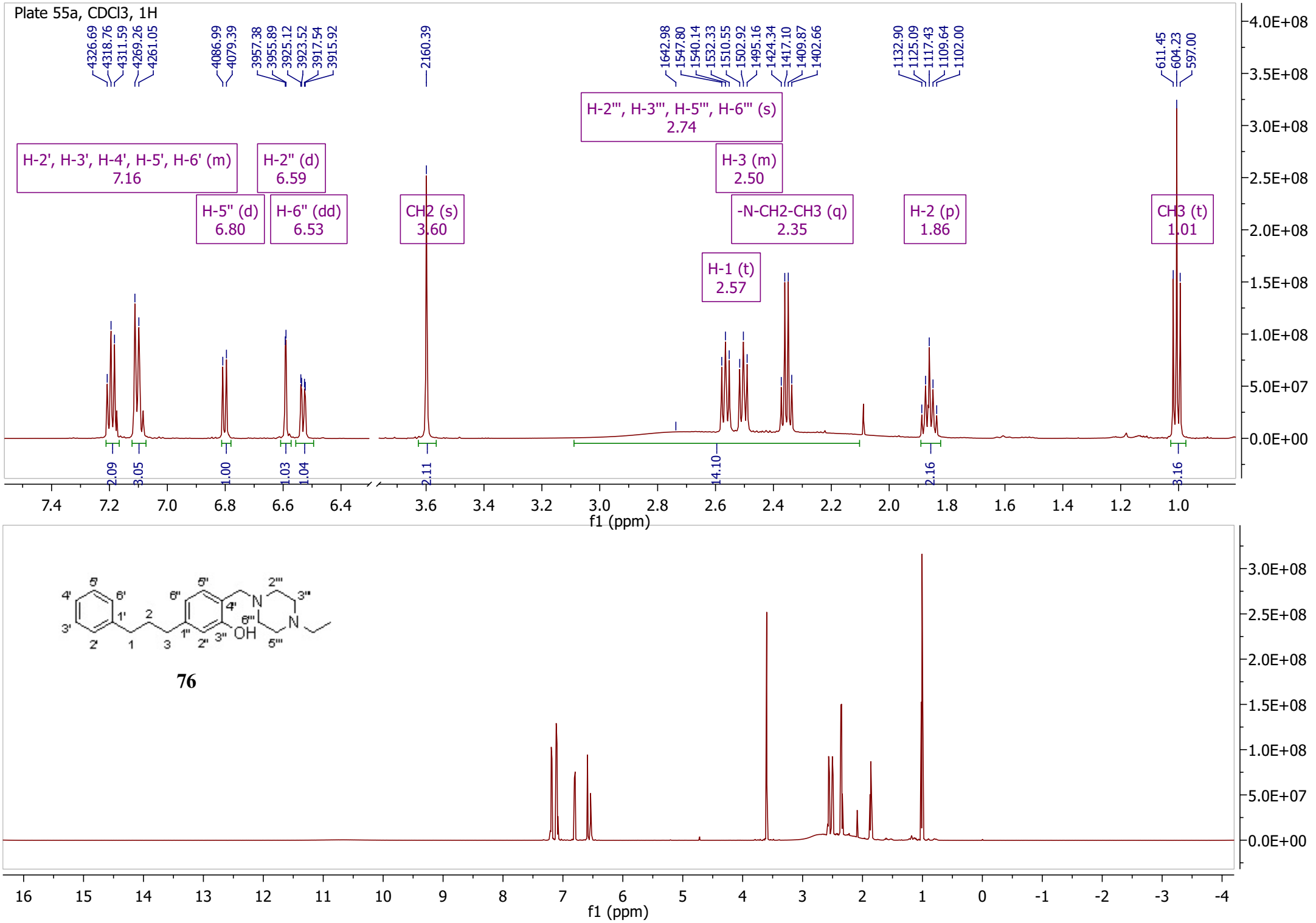


Plate 55a, CDCl3, 1H
4326.69
4318.76
4311.59
4269.26
4261.05
4086.99
4079.39
3957.38
3955.89
3925.12
3923.52
3917.54
3915.92
2160.39
1642.98
1547.80
1540.14
1532.33
1510.55
1502.92
1495.16
1424.34
1417.10
1409.87
1402.66
1132.90
1125.09
1117.43
1109.64
1102.00
611.45
604.23
597.00
H-2', H-3', H-4', H-5', H-6' (m)
7.16
H-2" (d)
6.59
H-5" (d)
6.80
H-6" (dd)
6.53
CH2 (s)
3.60
H-2‴, H-3‴, H-5‴, H-6‴ (s)
2.74
H-3 (m)
2.50
-N-CH2-CH3 (q)
2.35
H-1 (t)
2.57
H-2 (p)
1.86
CH3 (t)
1.01
2.09
3.05
1.00
1.03
1.04
2.11
14.10
2.16
3.16
f1 (ppm)
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
OH
N
76
f1 (ppm)

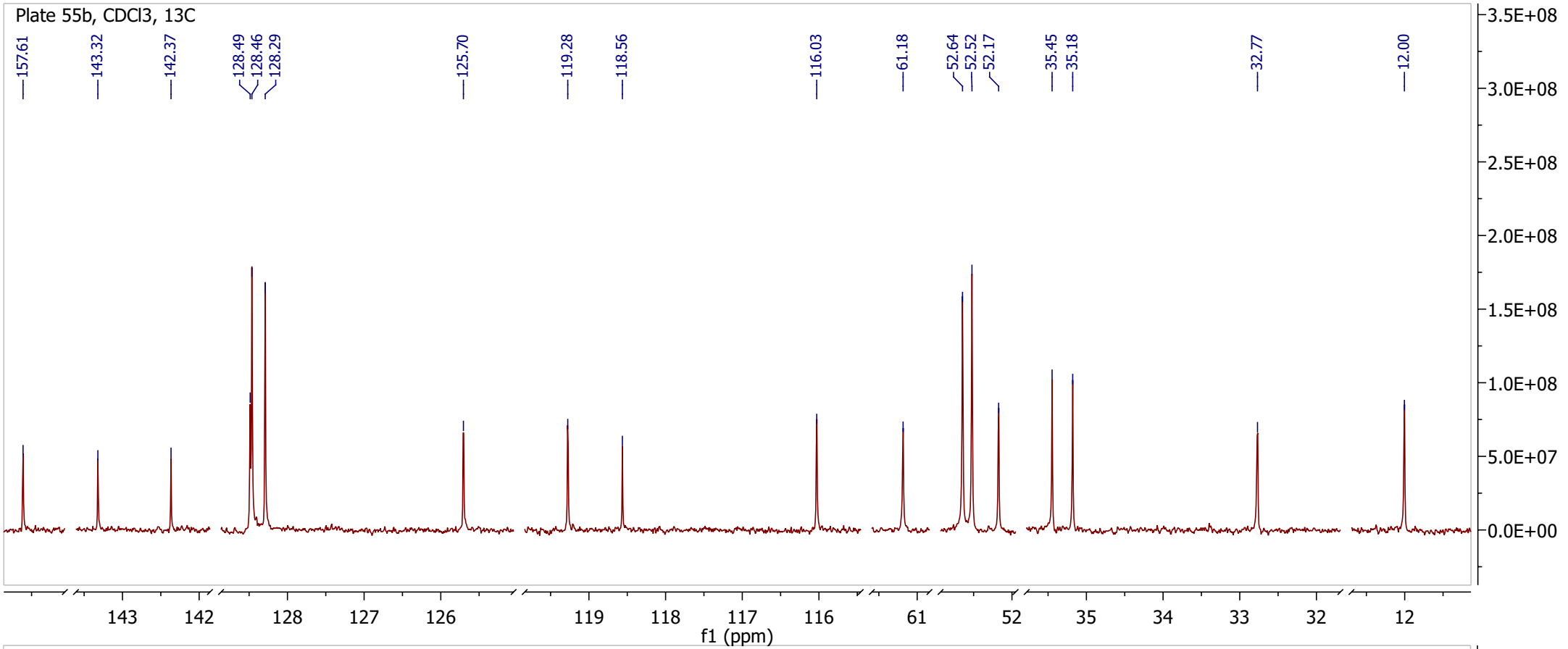
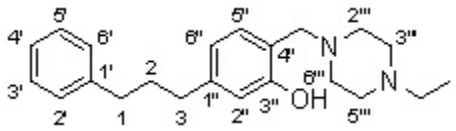


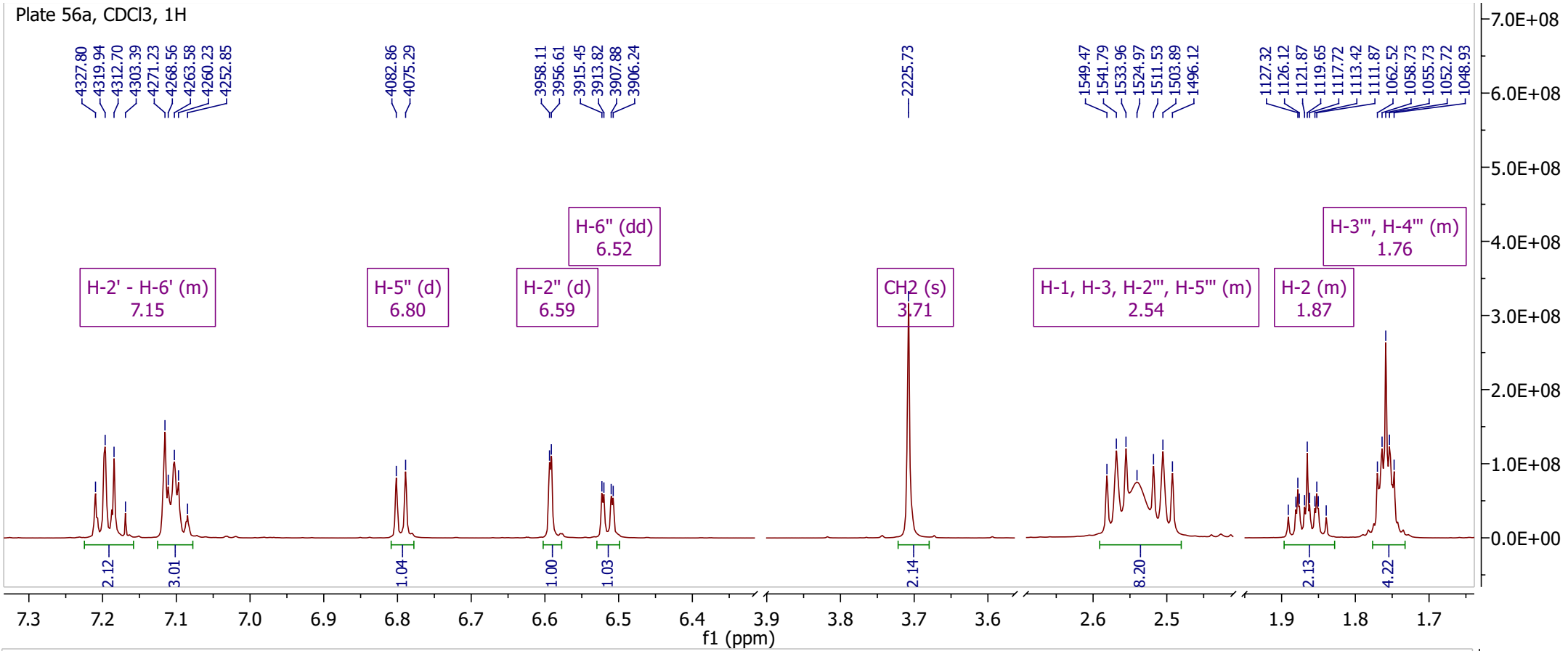
Plate 55b, CDCl3, 13C
157.61
143.32
142.37
128.49
128.46
128.29
125.70
119.28
118.56
116.03
61.18
52.64
52.52
52.17
35.45
35.18
32.77
12.00
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
143
142
128
127
126
119
118
117
116
61
52
35
34
33
32
12
f1 (ppm)

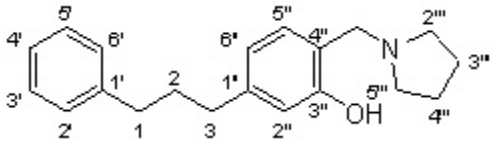

OH
N
N

76

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Plate 56a, CDCl3, 1H





77

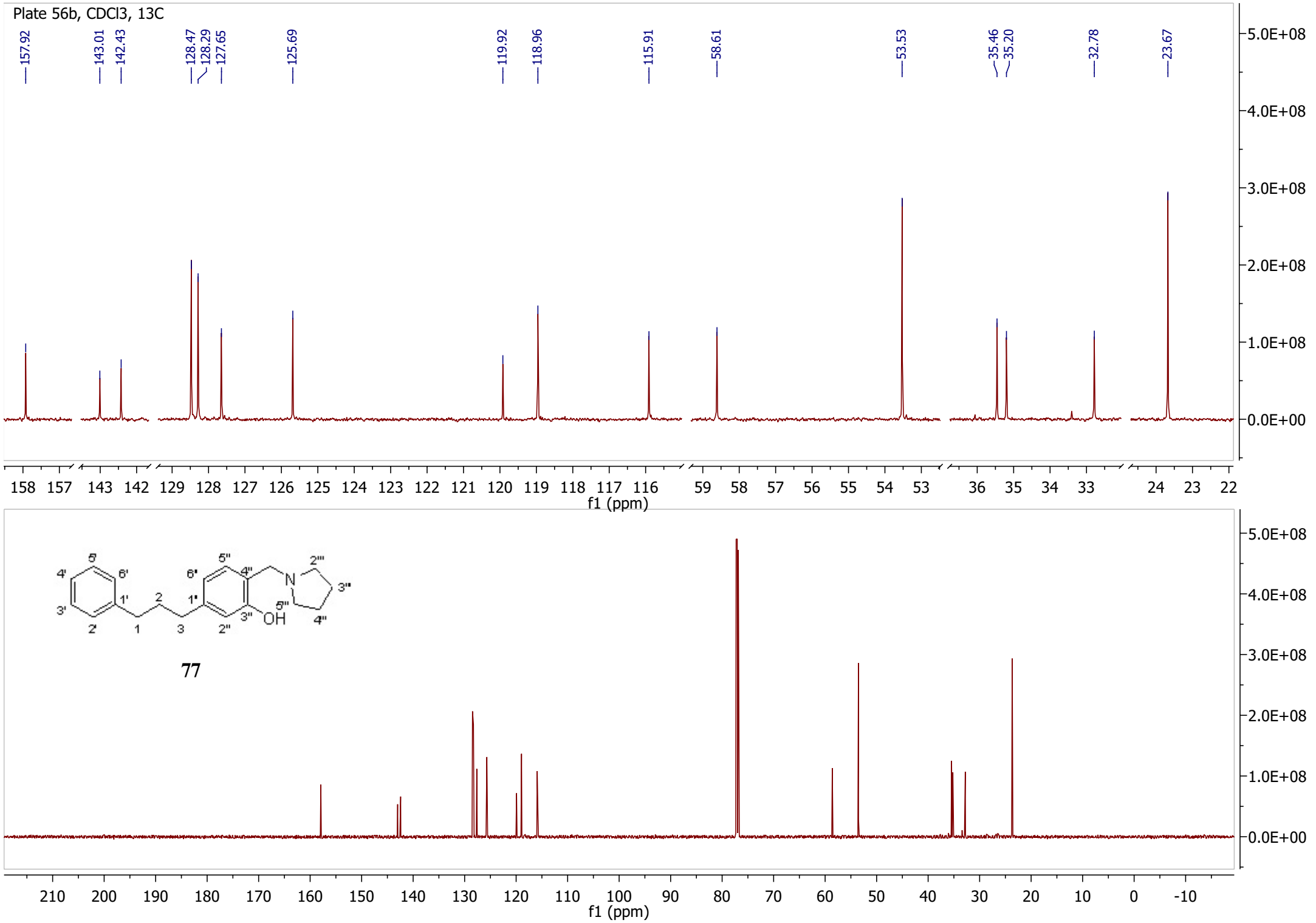


Plate 56b, CDCl3, 13C
157.92
143.01
142.43
128.47
128.29
127.65
125.69
119.92
118.96
115.91
58.61
53.53
35.46
35.20
32.78
23.67
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
158 157 143 142 129 128 127 126 125 124 123 122 121 120 119 118 117 116 59 58 57 56 55 54 53 36 35 34 33 24 23 22
f1 (ppm)
77
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

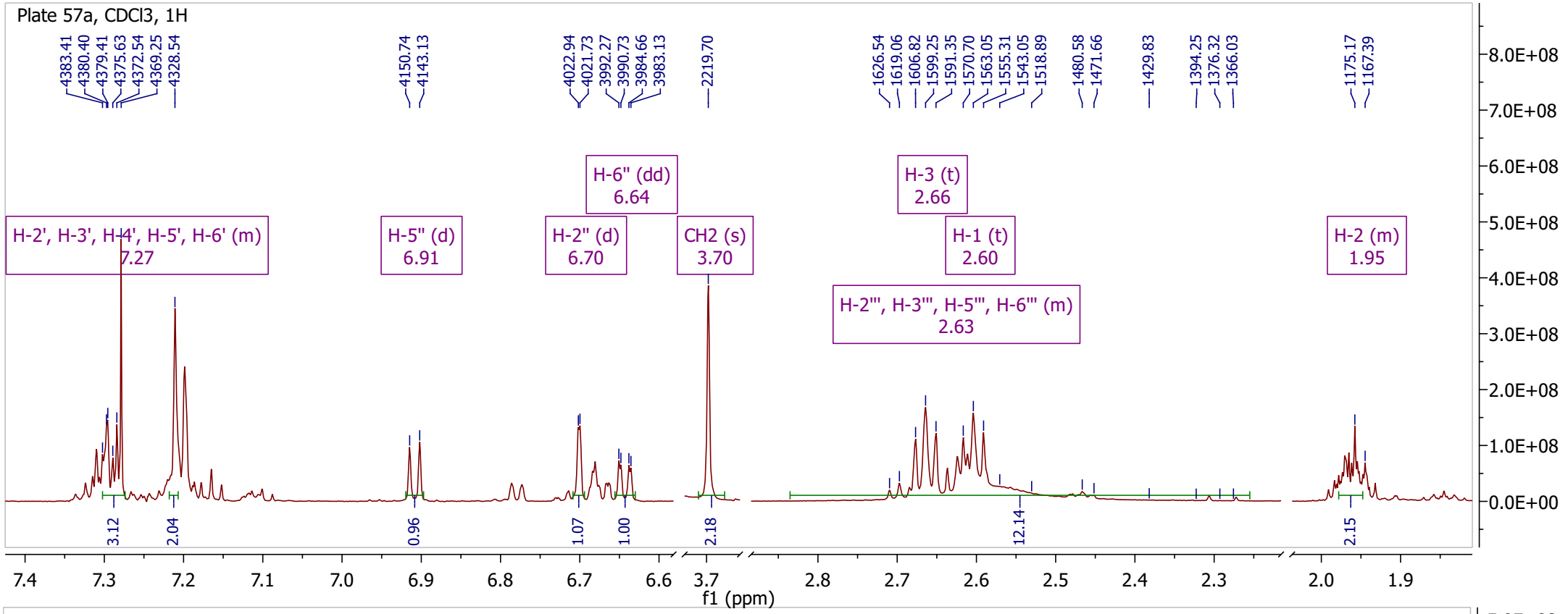
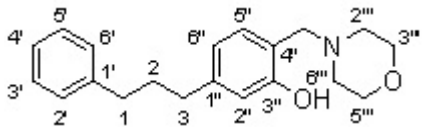


Plate 57a, CDCl3, 1H
4383.41
4380.40
4379.41
4375.63
4372.54
4369.25
4328.54
4150.74
4143.13
4022.94
4021.73
3992.27
3990.73
3984.66
3983.13
2219.70
1626.54
1619.06
1606.82
1599.25
1591.35
1570.70
1563.05
1555.31
1543.05
1518.89
1480.58
1471.66
1429.83
1394.25
1376.32
1366.03
1175.17
1167.39
H-2', H-3', H-4', H-5', H-6' (m)
7.27
H-5" (d)
6.91
H-6" (dd)
6.64
H-2" (d)
6.70
CH2 (s)
3.70
H-3 (t)
2.66
H-1 (t)
2.60
H-2"', H-3"', H-5"', H-6"' (m)
2.63
H-2 (m)
1.95
3.12
2.04
0.96
1.07
1.00
2.18
12.14
2.15
8.0E+08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
3.7
2.8
2.7
2.6
2.5
2.4
2.3
2.0
1.9
f1 (ppm)


5'
6'
4'
1'
2
3'
2'
1
3
6"
5'
4'
1"
2'
3"
OH
2'''
3"'
N
6'''
O
5'''

78

5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

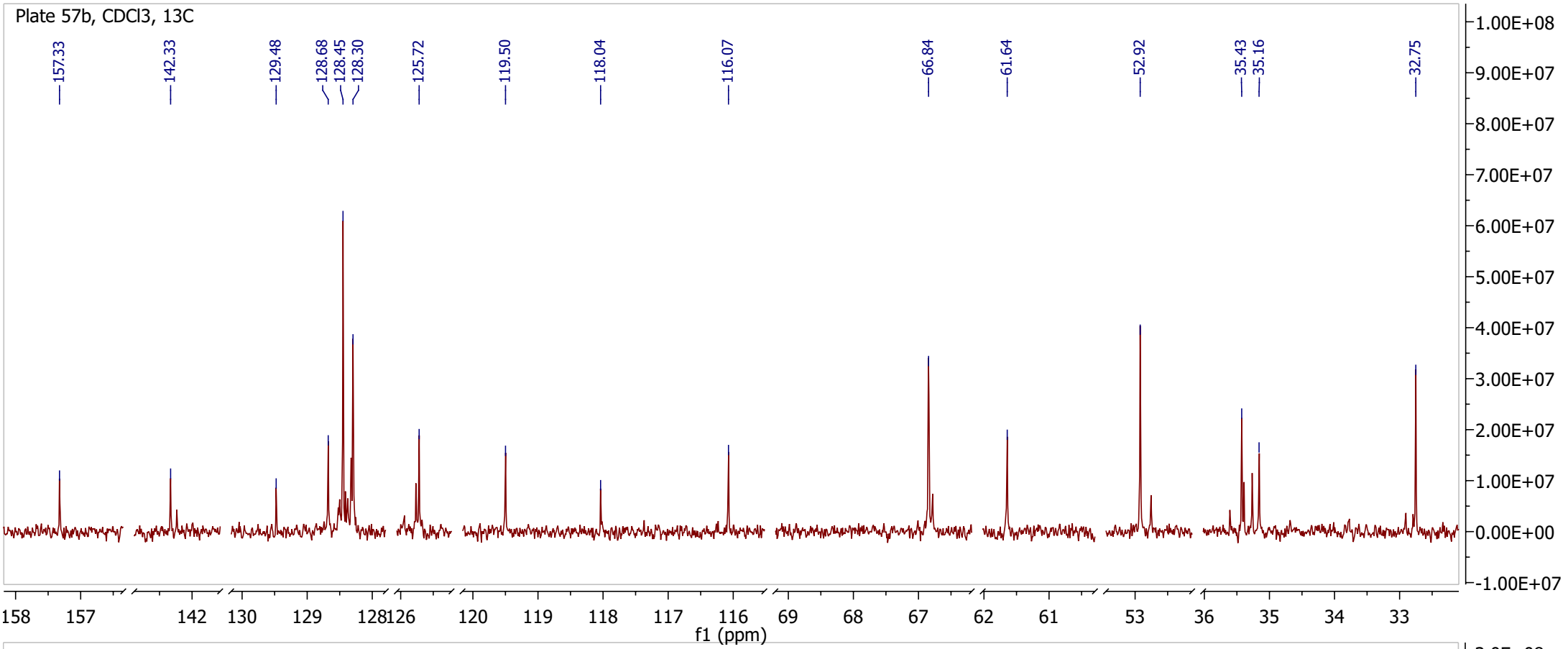
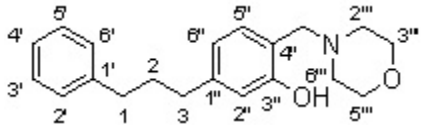


Plate 57b, CDCl3, 13C
157.33
142.33
129.48
128.68
128.45
128.30
125.72
119.50
118.04
116.07
66.84
61.64
52.92
35.43
35.16
32.75
f1 (ppm)


OH
N
O

78

f1 (ppm)

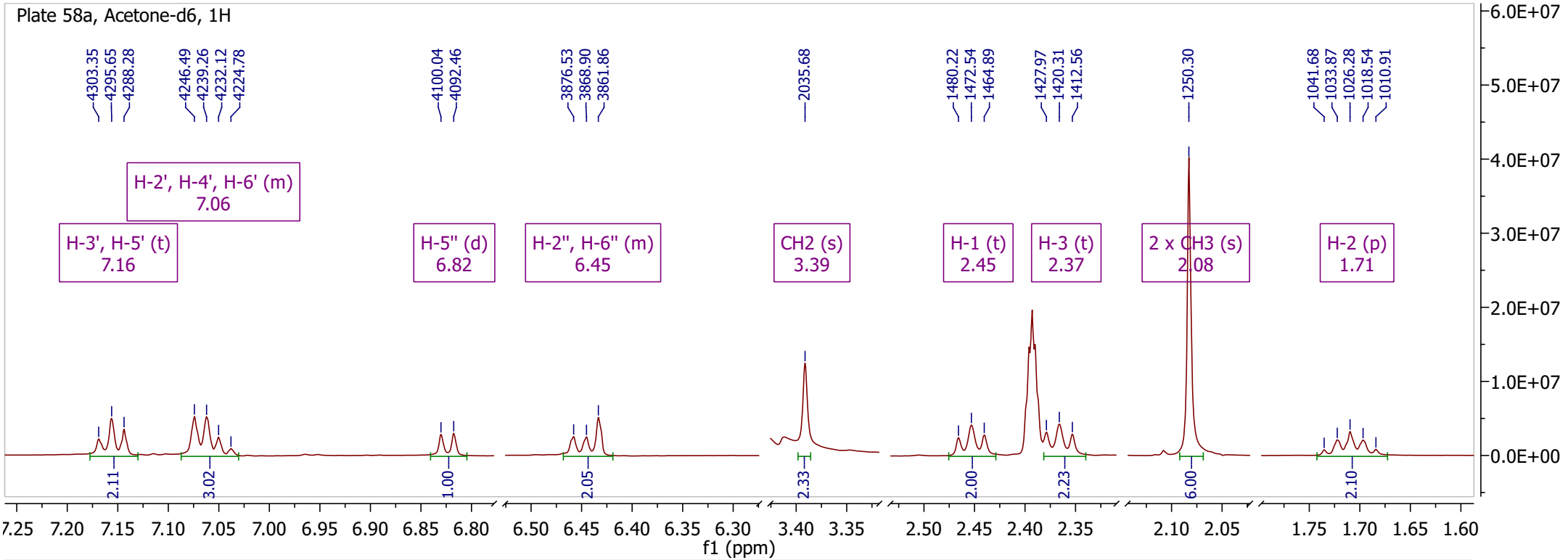
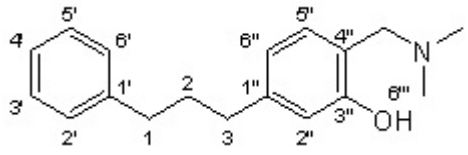


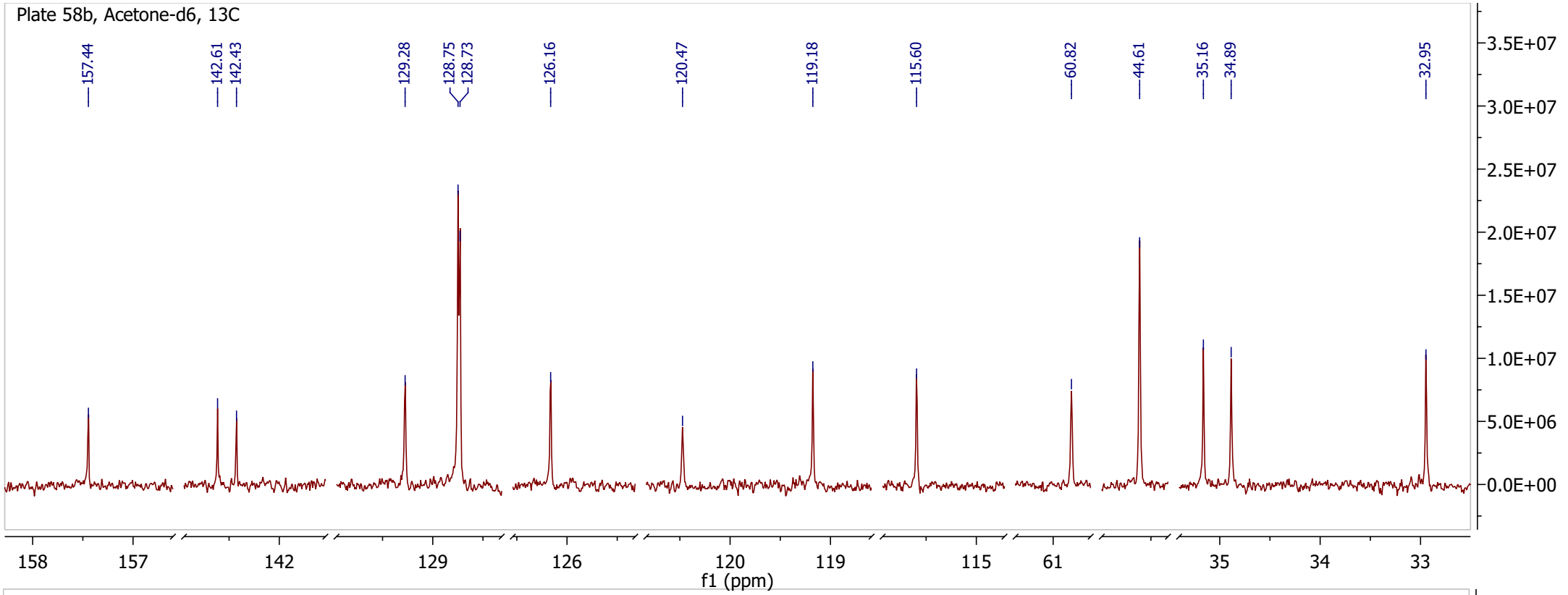
Plate 58a, Acetone-d6, 1H
4303.35
4295.65
4288.28
4246.49
4239.26
4232.12
4224.78
4100.04
4092.46
3876.53
3868.90
3861.86
2035.68
1480.22
1472.54
1464.89
1427.97
1420.31
1412.56
1250.30
1041.68
1033.87
1026.28
1018.54
1010.91
H-2', H-4', H-6' (m)
7.06
H-3', H-5' (t)
7.16
H-5" (d)
6.82
H-2", H-6" (m)
6.45
CH2 (s)
3.39
H-1 (t)
2.45
H-3 (t)
2.37
2 x CH3 (s)
2.08
H-2 (p)
1.71
2.11
3.02
1.00
2.05
2.33
2.00
2.23
6.00
2.10
f1 (ppm)

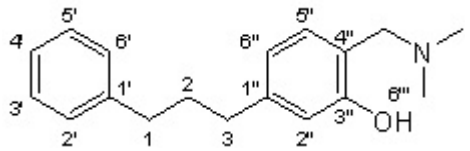

5'
4
6'
3'
1'
2
2'
1
3
6"
1"
5"
4"
N
6"'
3"
OH
2"

79

f1 (ppm)

Plate 58b, Acetone-d6, 13C





79

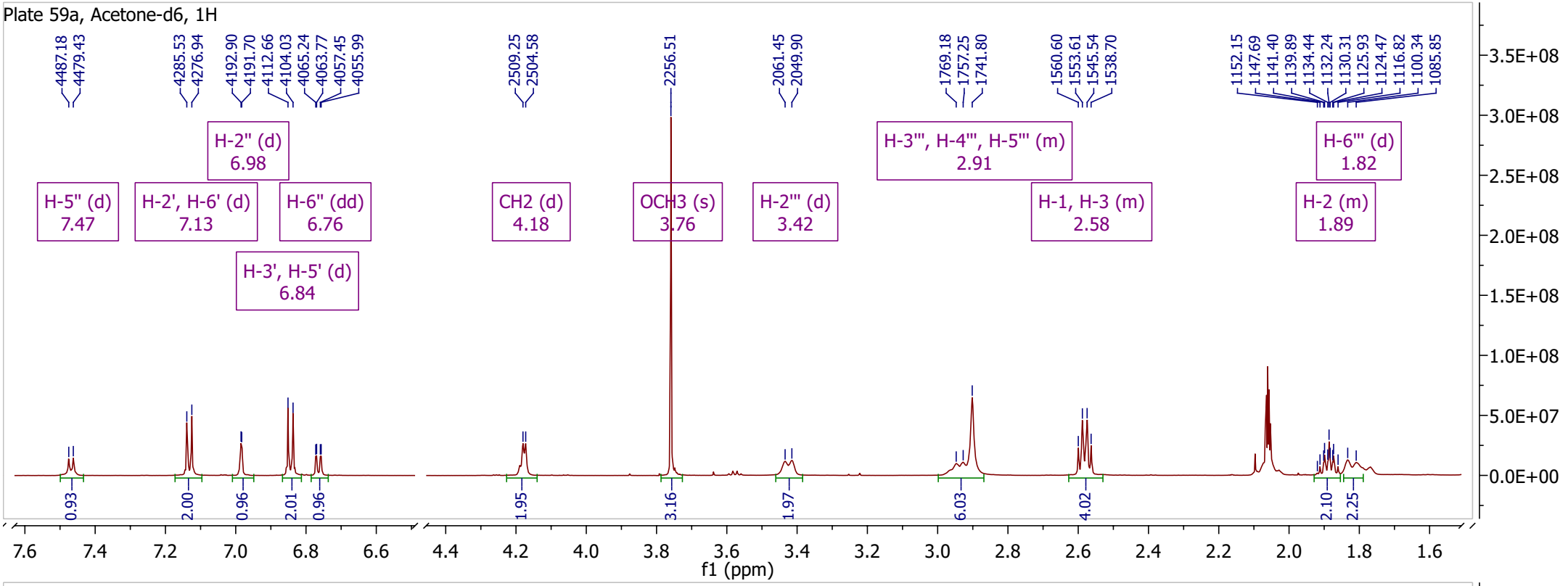
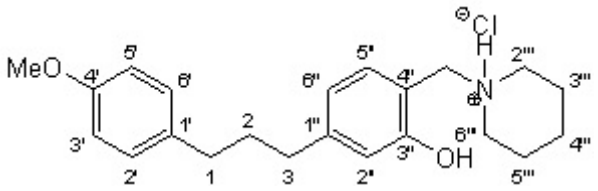


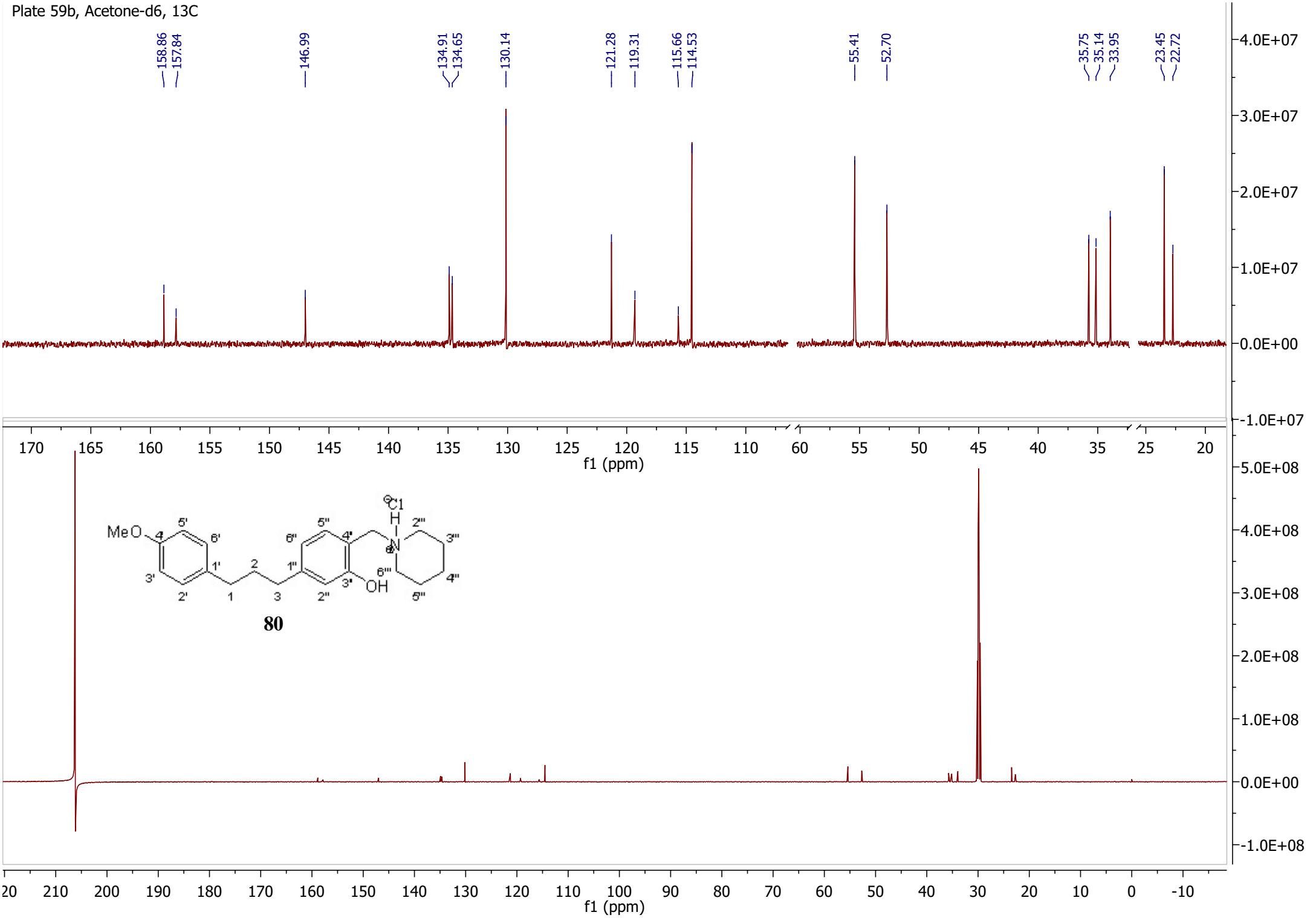
Plate 59a, Acetone-d6, 1H
4487.18
4479.43
4285.53
4276.94
4192.90
4191.70
4112.66
4104.03
4065.24
4063.77
4057.45
4055.99
2509.25
2504.58
2256.51
2061.45
2049.90
1769.18
1757.25
1741.80
1560.60
1553.61
1545.54
1538.70
1152.15
1147.69
1141.40
1139.89
1134.44
1132.24
1130.31
1125.93
1124.47
1116.82
1100.34
1085.85
H-5" (d)
7.47
H-2', H-6' (d)
7.13
H-2" (d)
6.98
H-6" (dd)
6.76
H-3', H-5' (d)
6.84
CH2 (d)
4.18
OCH3 (s)
3.76
H-2"' (d)
3.42
H-3"', H-4"', H-5"' (m)
2.91
H-1, H-3 (m)
2.58
H-6"' (d)
1.82
H-2 (m)
1.89
0.93
2.00
0.96
2.01
0.96
1.95
3.16
1.97
6.03
4.02
2.10
2.25
f1 (ppm)


MeO
Cl
H
N
OH

80

f1 (ppm)

Plate 59b, Acetone-d6, 13C



80

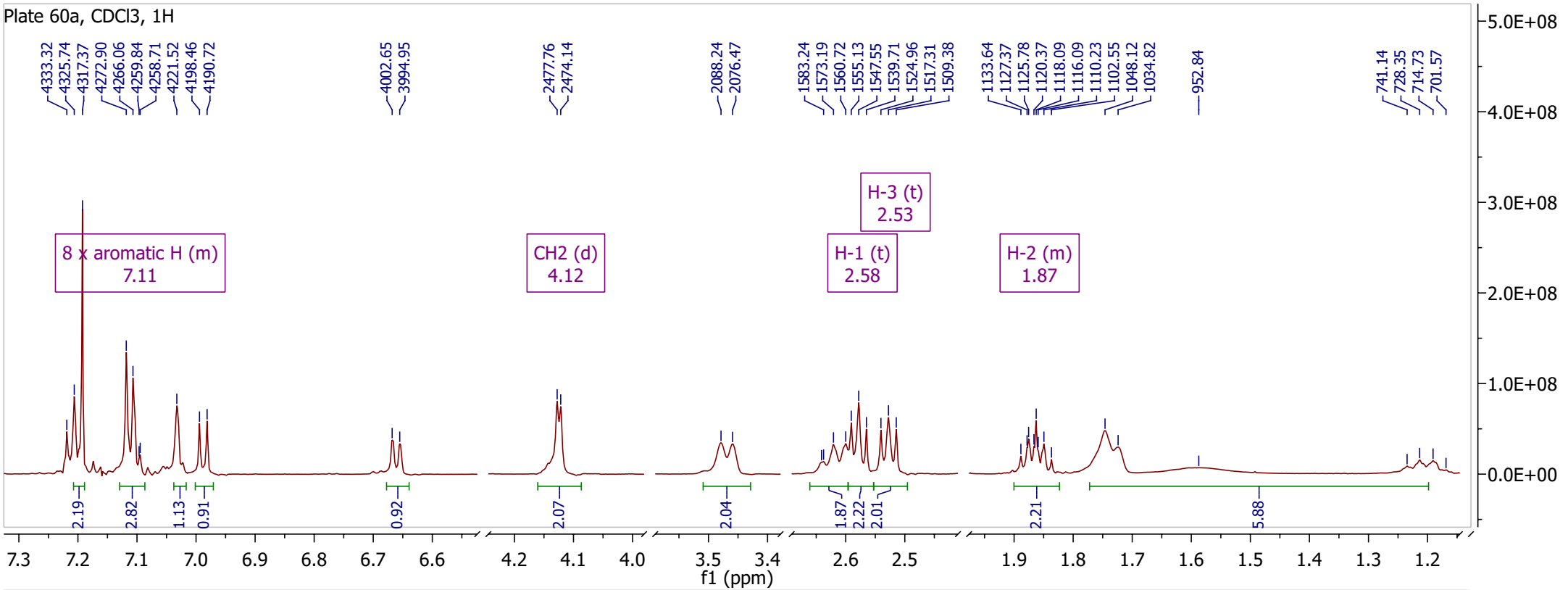
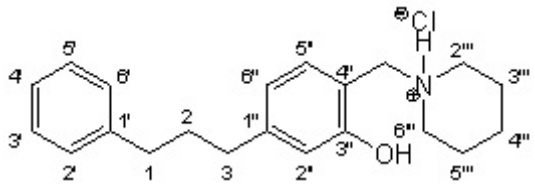


Plate 60a, CDCl3, 1H
4333.32
4325.74
4317.37
4272.90
4266.06
4259.84
4258.71
4221.52
4198.46
4190.72
4002.65
3994.95
2477.76
2474.14
2088.24
2076.47
1583.24
1573.19
1560.72
1555.13
1547.55
1539.71
1524.96
1517.31
1509.38
1133.64
1127.37
1125.78
1120.37
1118.09
1116.09
1110.23
1102.55
1048.12
1034.82
952.84
741.14
728.35
714.73
701.57
8 x aromatic H (m)
7.11
CH2 (d)
4.12
H-3 (t)
2.53
H-1 (t)
2.58
H-2 (m)
1.87
2.19
2.82
1.13
0.91
0.92
2.07
2.04
1.87
2.22
2.01
2.21
5.88
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
4.2
4.1
4.0
3.5
3.4
2.6
2.5
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
f1 (ppm)


Cl
H
N
OH

82

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

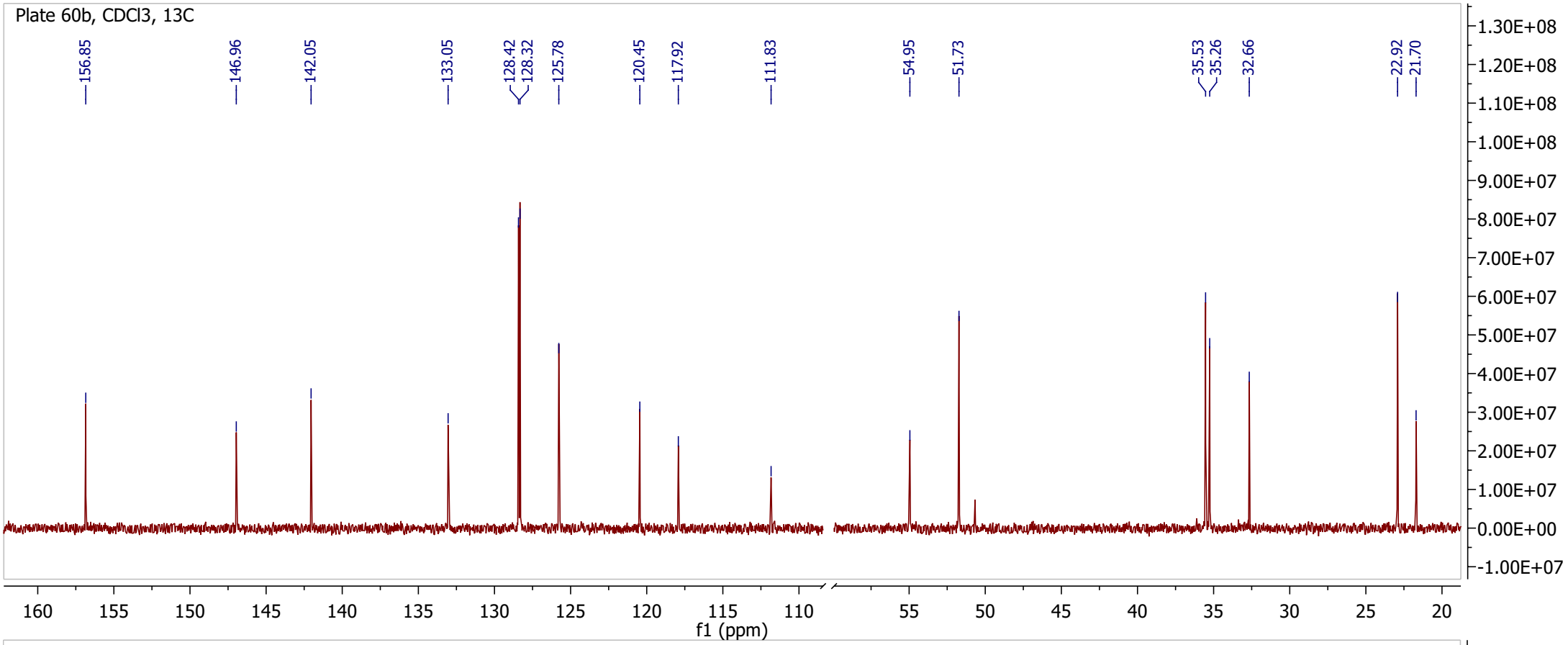
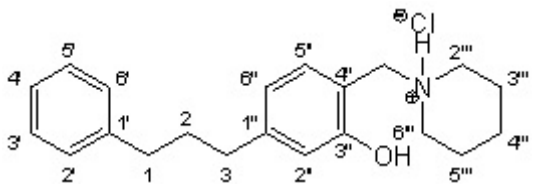


Plate 60b, CDCl3, 13C
156.85
146.96
142.05
133.05
128.42
128.32
125.78
120.45
117.92
111.83
54.95
51.73
35.53
35.26
32.66
22.92
21.70
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
160 155 150 145 140 135 130 125 120 115 110 55 50 45 40 35 30 25 20
f1 (ppm)


Cl
H
N
OH

82

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

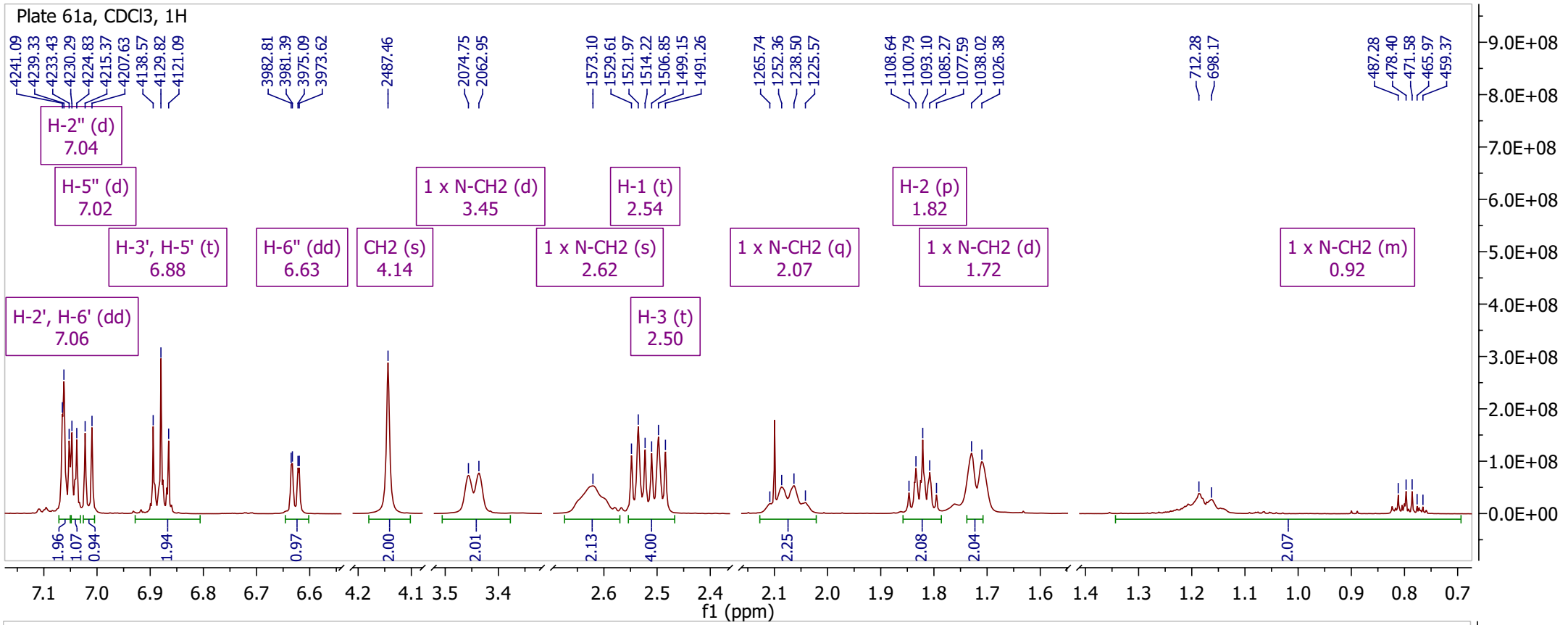
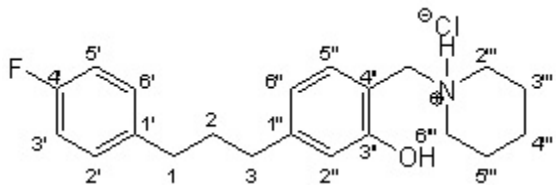


Plate 61a, CDCl3, 1H
4241.09
4239.33
4233.43
4230.29
4224.83
4215.37
4207.63
4138.57
4129.82
4121.09
3982.81
3981.39
3975.09
3973.62
2487.46
2074.75
2062.95
1573.10
1529.61
1521.97
1514.22
1506.85
1499.15
1491.26
1265.74
1252.36
1238.50
1225.57
1108.64
1100.79
1093.10
1085.27
1077.59
1038.02
1026.38
712.28
698.17
487.28
478.40
471.58
465.97
459.37
H-2" (d) 7.04
H-5" (d) 7.02
H-3', H-5' (t) 6.88
H-6" (dd) 6.63
CH2 (s) 4.14
1 x N-CH2 (d) 3.45
1 x N-CH2 (s) 2.62
H-1 (t) 2.54
H-3 (t) 2.50
1 x N-CH2 (q) 2.07
H-2 (p) 1.82
1 x N-CH2 (d) 1.72
1 x N-CH2 (m) 0.92
H-2', H-6' (dd) 7.06
1.96
1.07
0.94
1.94
0.97
2.00
2.01
2.13
4.00
2.25
2.08
2.04
2.07
9.0E+08
8.0E+08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.1 7.0 6.9 6.8 6.7 6.6 4.2 4.1 3.5 3.4 2.6 2.5 2.4 2.1 2.0 1.9 1.8 1.7 1.6 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7
f1 (ppm)


F
Cl
H
N
OH
5'
6'
4'
1'
2
3'
2'
1
3
1"
2"
3"
4"
5"
6"

81

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

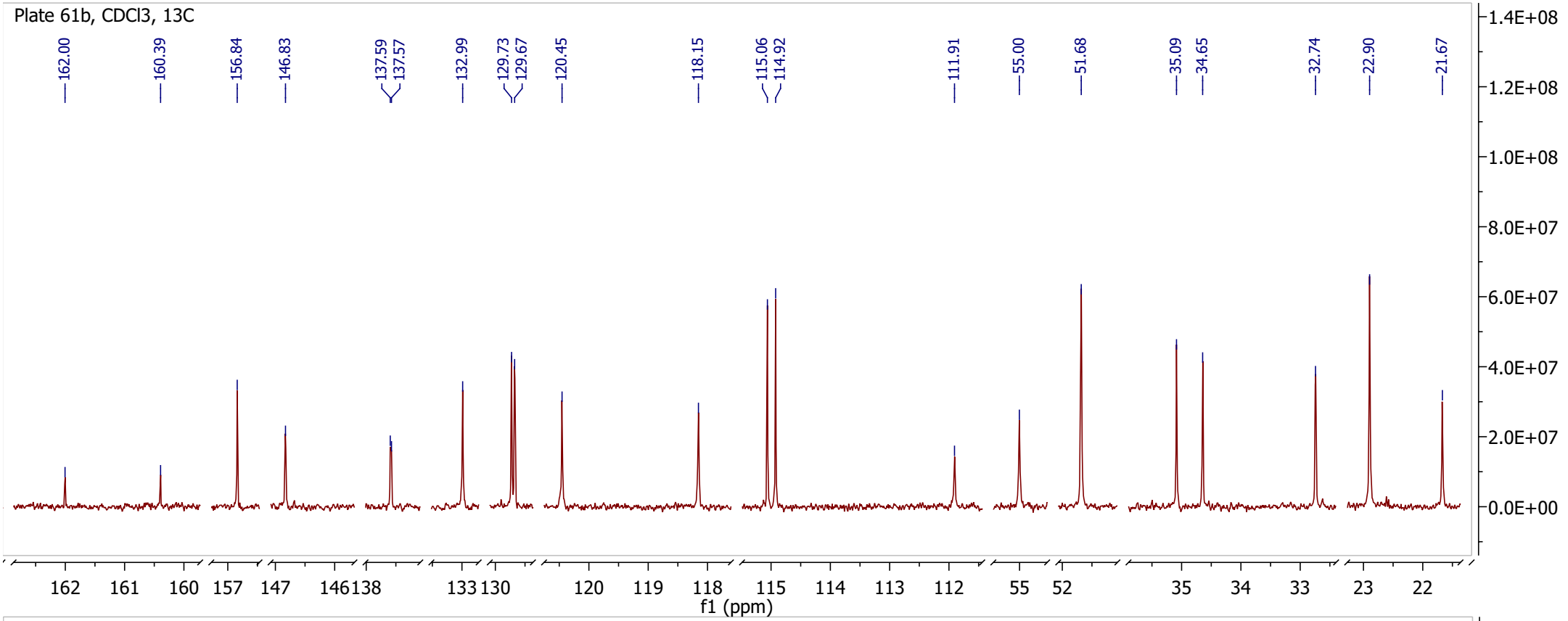
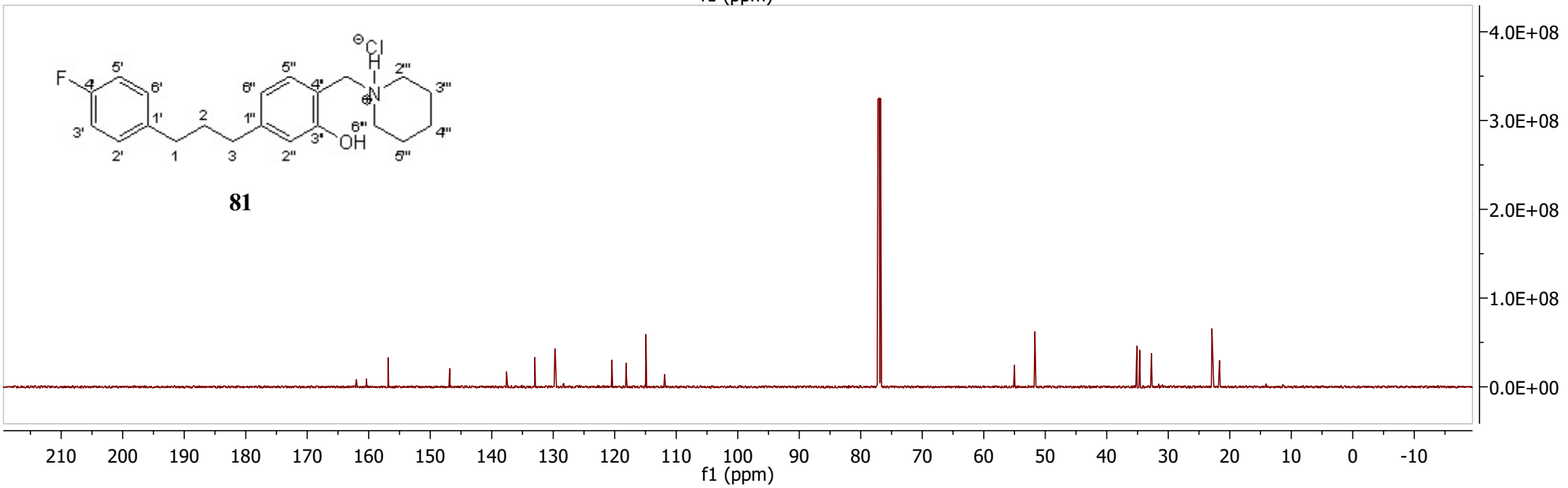


Plate 61b, CDCl3, 13C
162.00
160.39
156.84
146.83
137.59
137.57
132.99
129.73
129.67
120.45
118.15
115.06
114.92
111.91
55.00
51.68
35.09
34.65
32.74
22.90
21.67
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
162 161 160 157 147 146 138 133 130 120 119 118 115 114 113 112 55 52 35 34 33 23 22
f1 (ppm)


F
Cl
H
N
OH
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

81

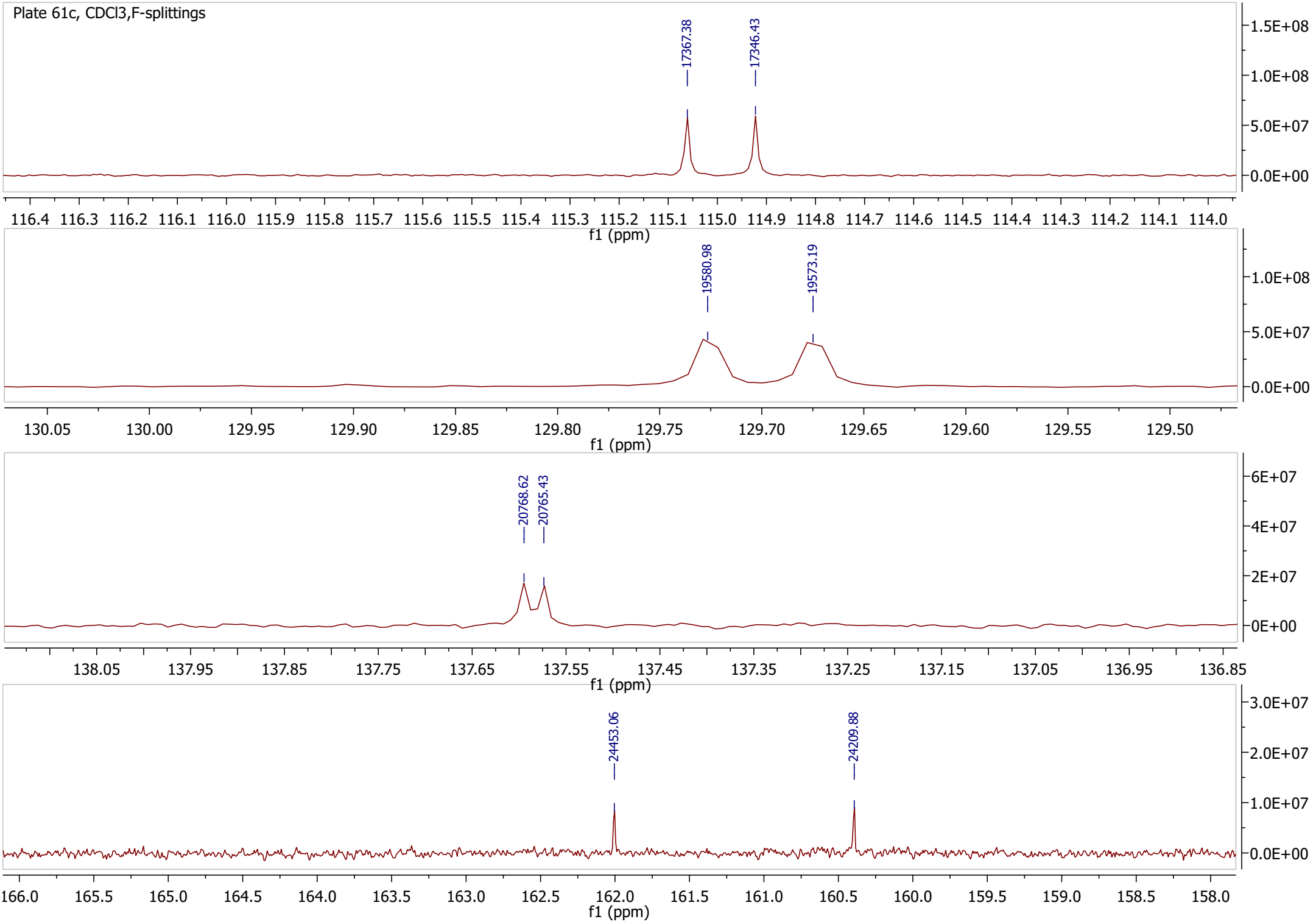
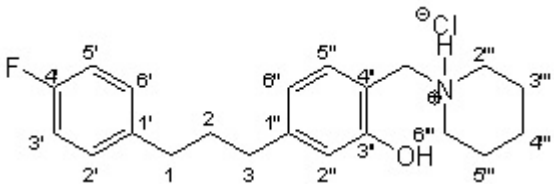


Plate 61c, CDCl3,F-splittings
17367.38
17346.43
1.5E+08
1.0E+08
5.0E+07
0.0E+00
116.4 116.3 116.2 116.1 116.0 115.9 115.8 115.7 115.6 115.5 115.4 115.3 115.2 115.1 115.0 114.9 114.8 114.7 114.6 114.5 114.4 114.3 114.2 114.1 114.0
f1 (ppm)
19580.98
19573.19
1.0E+08
5.0E+07
0.0E+00
130.05 130.00 129.95 129.90 129.85 129.80 129.75 129.70 129.65 129.60 129.55 129.50
f1 (ppm)
20768.62
20765.43
6E+07
4E+07
2E+07
0E+00
138.05 137.95 137.85 137.75 137.65 137.55 137.45 137.35 137.25 137.15 137.05 136.95 136.85
f1 (ppm)
24453.06
24209.88
3.0E+07
2.0E+07
1.0E+07
0.0E+00
166.0 165.5 165.0 164.5 164.0 163.5 163.0 162.5 162.0 161.5 161.0 160.5 160.0 159.5 159.0 158.5 158.0
f1 (ppm)

Plate 61d, CDCl3, 19F



81

-117.85

1.90E+09
1.80E+09
1.70E+09
1.60E+09
1.50E+09
1.40E+09
1.30E+09
1.20E+09
1.10E+09
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
-1.00E+08
-2.00E+08
-3.00E+08
-4.00E+08

00 50 0 -50 -100 -150 -200 -250 -300

f1 (ppm)

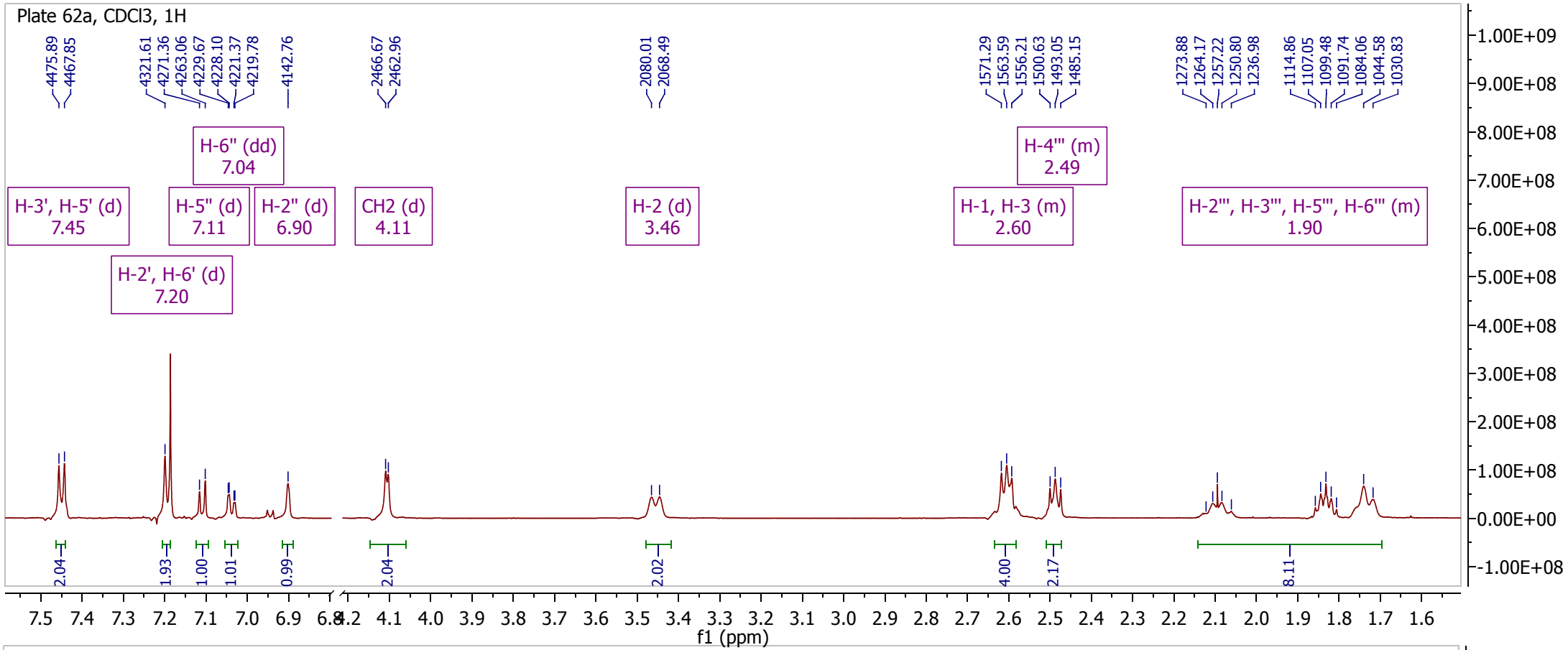
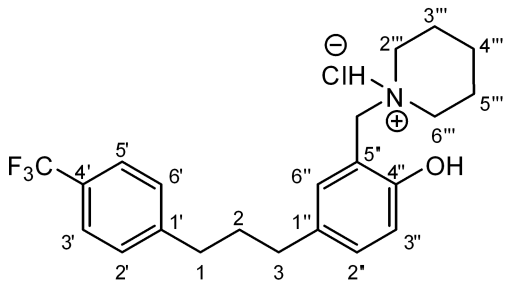


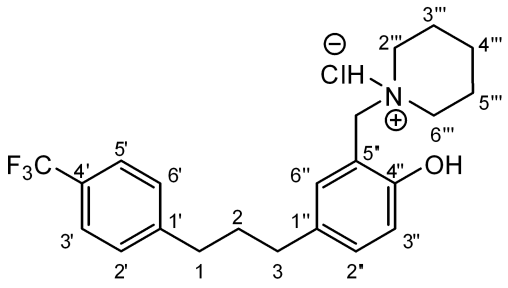
Plate 62a, CDCl3, 1H
4475.89
4467.85
4321.61
4271.36
4263.06
4229.67
4228.10
4221.37
4219.78
4142.76
2466.67
2462.96
2080.01
2068.49
1571.29
1563.59
1556.21
1500.63
1493.05
1485.15
1273.88
1264.17
1257.22
1250.80
1236.98
1114.86
1107.05
1099.48
1091.74
1084.06
1044.58
1030.83
H-6" (dd)
7.04
H-4''' (m)
2.49
H-3', H-5' (d)
7.45
H-5" (d)
7.11
H-2" (d)
6.90
CH2 (d)
4.11
H-2 (d)
3.46
H-1, H-3 (m)
2.60
H-2''', H-3''', H-5''', H-6''' (m)
1.90
H-2', H-6' (d)
7.20
2.04
1.93
1.00
1.01
0.99
2.04
2.02
4.00
2.17
8.11
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
-1.00E+08
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6
f1 (ppm)


ClH
N
F3C
OH
3'''
2'''
4'''
5'''
6'''
5'
6'
4'
1'
2
1''
6''
5''
4''
3''
3'
2'
1
3
2''

83

1.2E+09
1.0E+09
8.0E+08
6.0E+08
4.0E+08
2.0E+08
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

Plate 62b, CDCl3, 19F



83

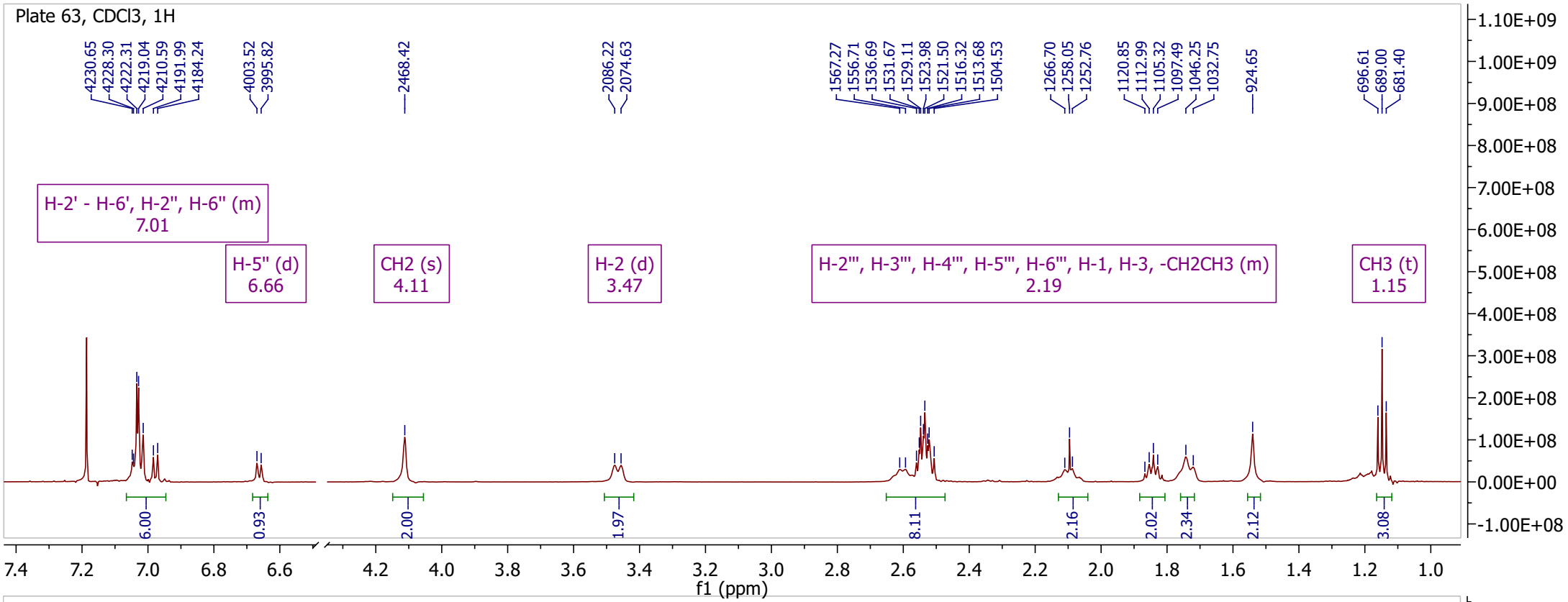
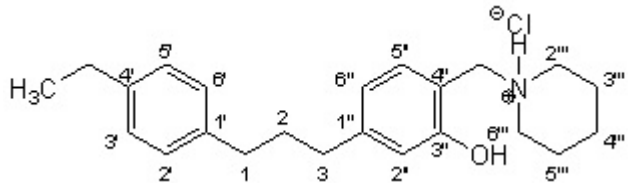


Plate 63, CDCl3, 1H
4230.65
4228.30
4222.31
4219.04
4210.59
4191.99
4184.24
4003.52
3995.82
2468.42
2086.22
2074.63
1567.27
1556.71
1536.69
1531.67
1529.11
1523.98
1521.50
1516.32
1513.68
1504.53
1266.70
1258.05
1252.76
1120.85
1112.99
1105.32
1097.49
1046.25
1032.75
924.65
696.61
689.00
681.40
H-2' - H-6', H-2", H-6" (m)
7.01
H-5" (d)
6.66
CH2 (s)
4.11
H-2 (d)
3.47
H-2"', H-3"', H-4"', H-5"', H-6"', H-1, H-3, -CH2CH3 (m)
2.19
CH3 (t)
1.15
6.00
0.93
2.00
1.97
8.11
2.16
2.02
2.34
2.12
3.08
f1 (ppm)


H3C
Cl
H
N
OH

84

f1 (ppm)

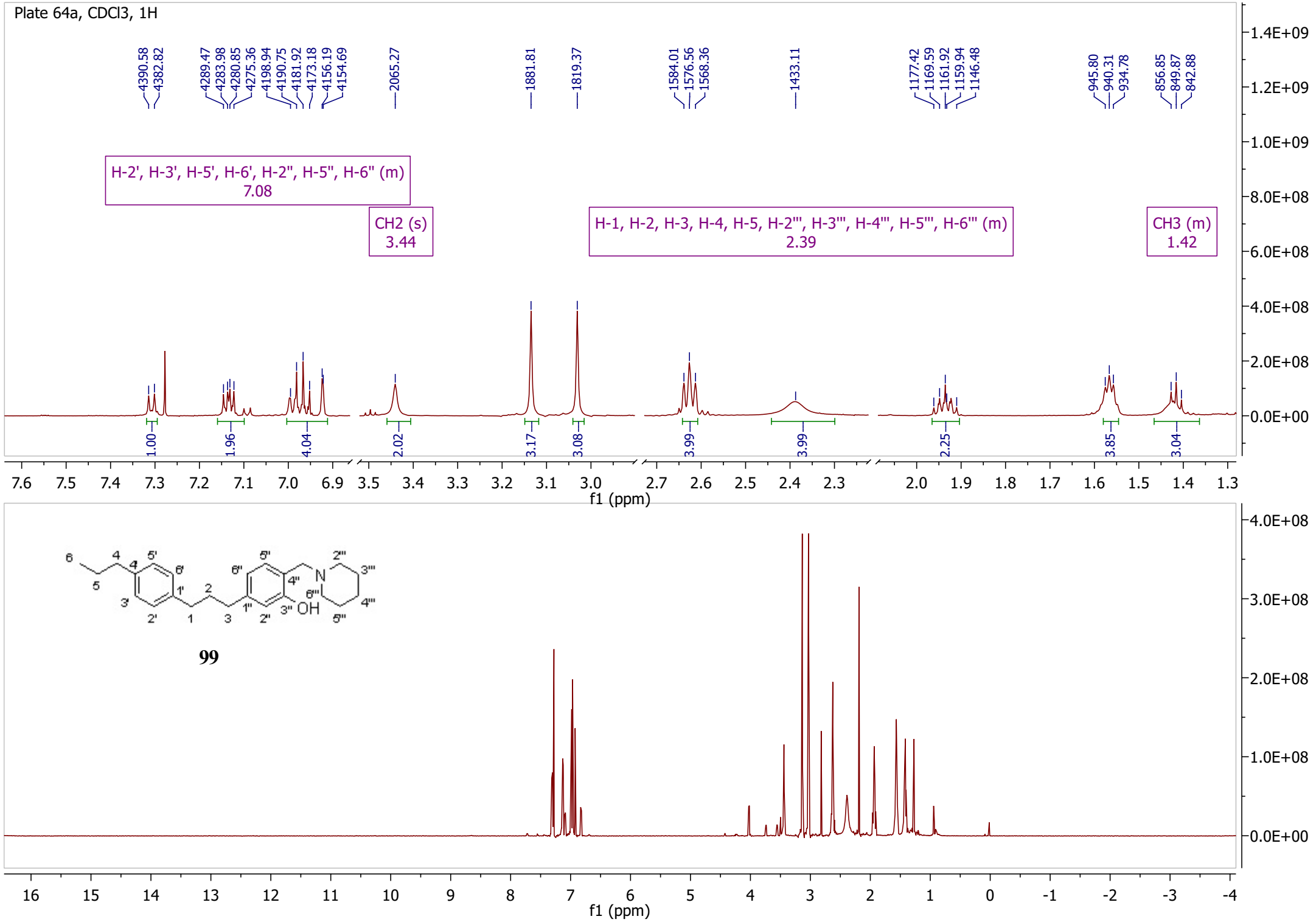


Plate 64a, CDCl3, 1H
4390.58
4382.82
4289.47
4283.98
4280.85
4275.36
4198.94
4190.75
4181.92
4173.18
4156.19
4154.69
2065.27
1881.81
1819.37
1584.01
1576.56
1568.36
1433.11
1177.42
1169.59
1161.92
1159.94
1146.48
945.80
940.31
934.78
856.85
849.87
842.88
H-2', H-3', H-5', H-6', H-2", H-5", H-6" (m)
7.08
CH2 (s)
3.44
H-1, H-2, H-3, H-4, H-5, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴ (m)
2.39
CH3 (m)
1.42
1.00
1.96
4.04
2.02
3.17
3.08
3.99
3.99
2.25
3.85
3.04
f1 (ppm)
99
f1 (ppm)

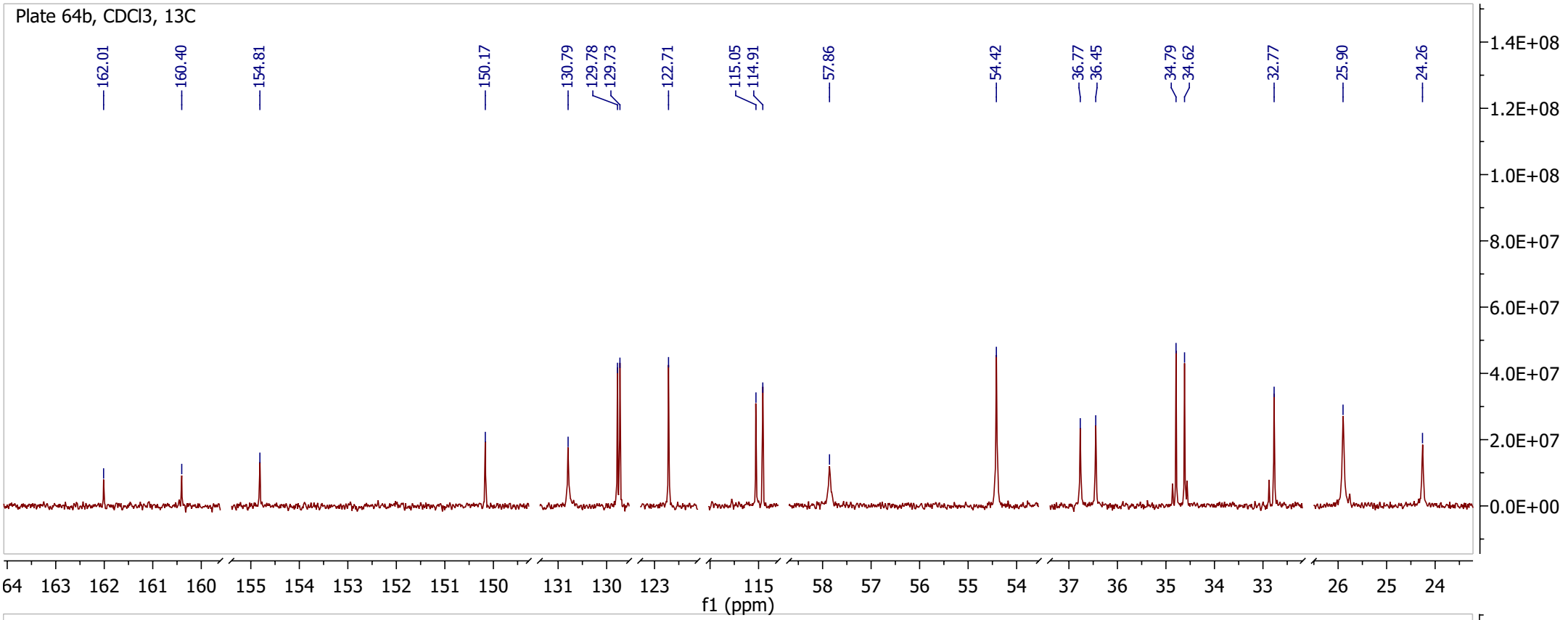
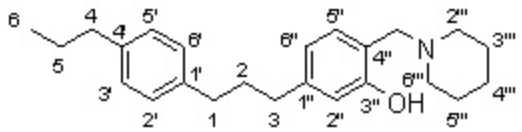


Plate 64b, CDCl3, 13C
162.01
160.40
154.81
150.17
130.79
129.78
129.73
122.71
115.05
114.91
57.86
54.42
36.77
36.45
34.79
34.62
32.77
25.90
24.26
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
64 163 162 161 160 155 154 153 152 151 150 131 130 123 115 58 57 56 55 54 37 36 35 34 33 26 25 24
f1 (ppm)


6
4
5'
4
5
6'
1'
2
3'
2'
1
3
6"
5'
4"
1"
2'
3"
OH
N
2"
3"'
6"'
4"'
5"

99

6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

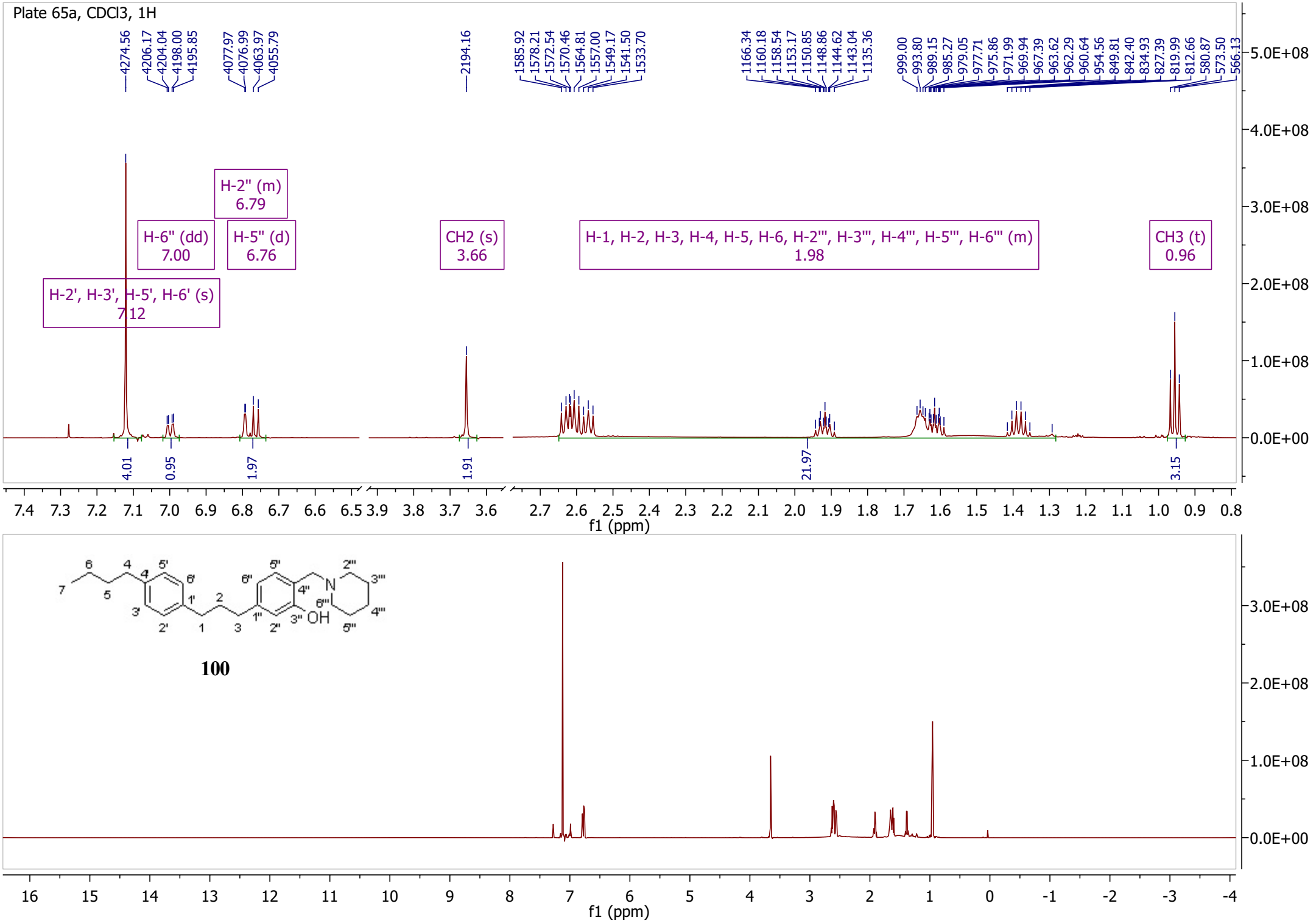
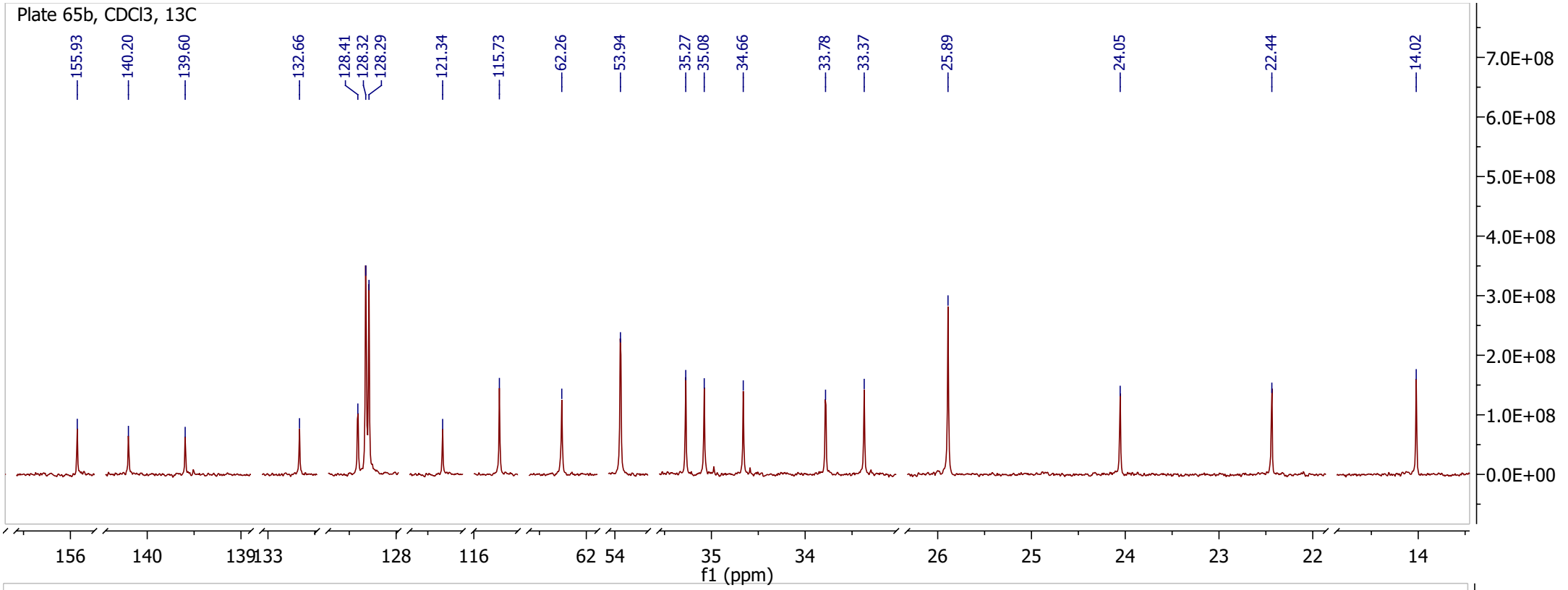
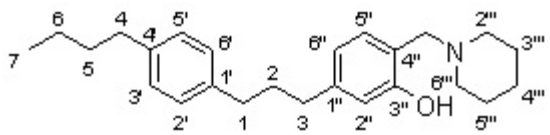


Plate 65a, CDCl3, 1H
4274.56
4206.17
4204.04
4198.00
4195.85
4077.97
4076.99
4063.97
4055.79
2194.16
1585.92
1578.21
1572.54
1570.46
1564.81
1557.00
1549.17
1541.50
1533.70
1166.34
1160.18
1158.54
1153.17
1150.85
1148.86
1144.62
1143.04
1135.36
999.00
993.80
989.15
985.27
979.05
977.71
975.86
971.99
969.94
967.39
963.62
962.29
960.64
954.56
849.81
842.40
834.93
827.39
819.99
812.66
580.87
573.50
566.13
H-2" (m)
6.79
H-6" (dd)
7.00
H-5" (d)
6.76
CH2 (s)
3.66
H-1, H-2, H-3, H-4, H-5, H-6, H-2'", H-3'", H-4'", H-5'", H-6'" (m)
1.98
CH3 (t)
0.96
H-2', H-3', H-5', H-6' (s)
7.12
4.01
0.95
1.97
1.91
21.97
3.15
f1 (ppm)
100
f1 (ppm)

Plate 65b, CDCl3, 13C





100

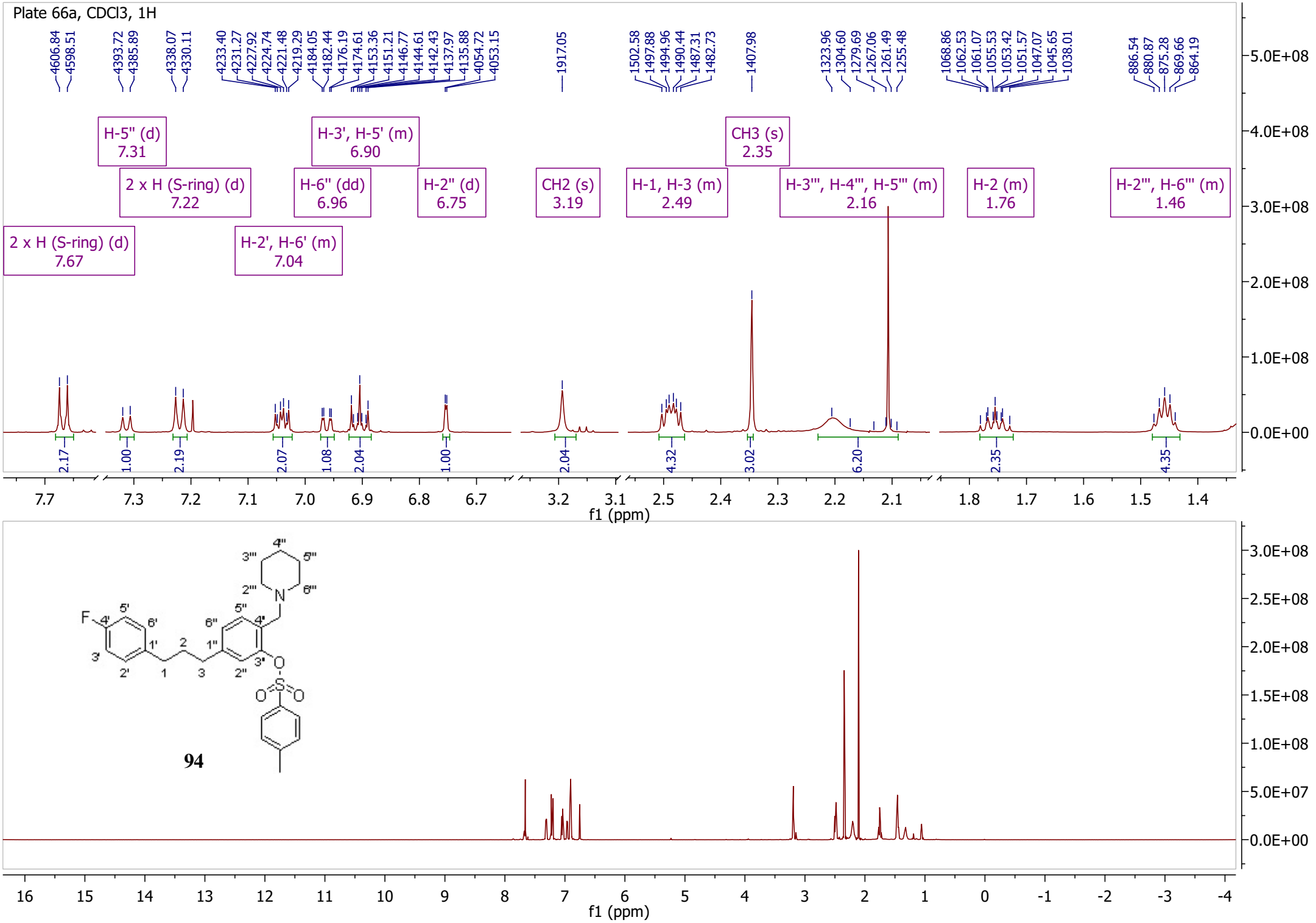


Plate 66a, CDCl3, 1H
4606.84
4598.51
4393.72
4385.89
4338.07
4330.11
4233.40
4231.27
4227.92
4224.74
4221.48
4219.29
4184.05
4182.44
4176.19
4174.61
4153.36
4151.21
4146.77
4144.61
4142.43
4137.97
4135.88
4054.72
4053.15
1917.05
1502.58
1497.88
1494.96
1490.44
1487.31
1482.73
1407.98
1323.96
1304.60
1279.69
1267.06
1261.49
1255.48
1068.86
1062.53
1061.07
1055.53
1053.42
1051.57
1047.07
1045.65
1038.01
886.54
880.87
875.28
869.66
864.19
H-5" (d)
7.31
2 x H (S-ring) (d)
7.22
2 x H (S-ring) (d)
7.67
H-2', H-6' (m)
7.04
H-3', H-5' (m)
6.90
H-6" (dd)
6.96
H-2" (d)
6.75
CH2 (s)
3.19
CH3 (s)
2.35
H-1, H-3 (m)
2.49
H-3"', H-4"', H-5"' (m)
2.16
H-2 (m)
1.76
H-2"', H-6"' (m)
1.46
2.17
1.00
2.19
2.07
1.08
2.04
1.00
2.04
4.32
3.02
6.20
2.35
4.35
f1 (ppm)
94
f1 (ppm)

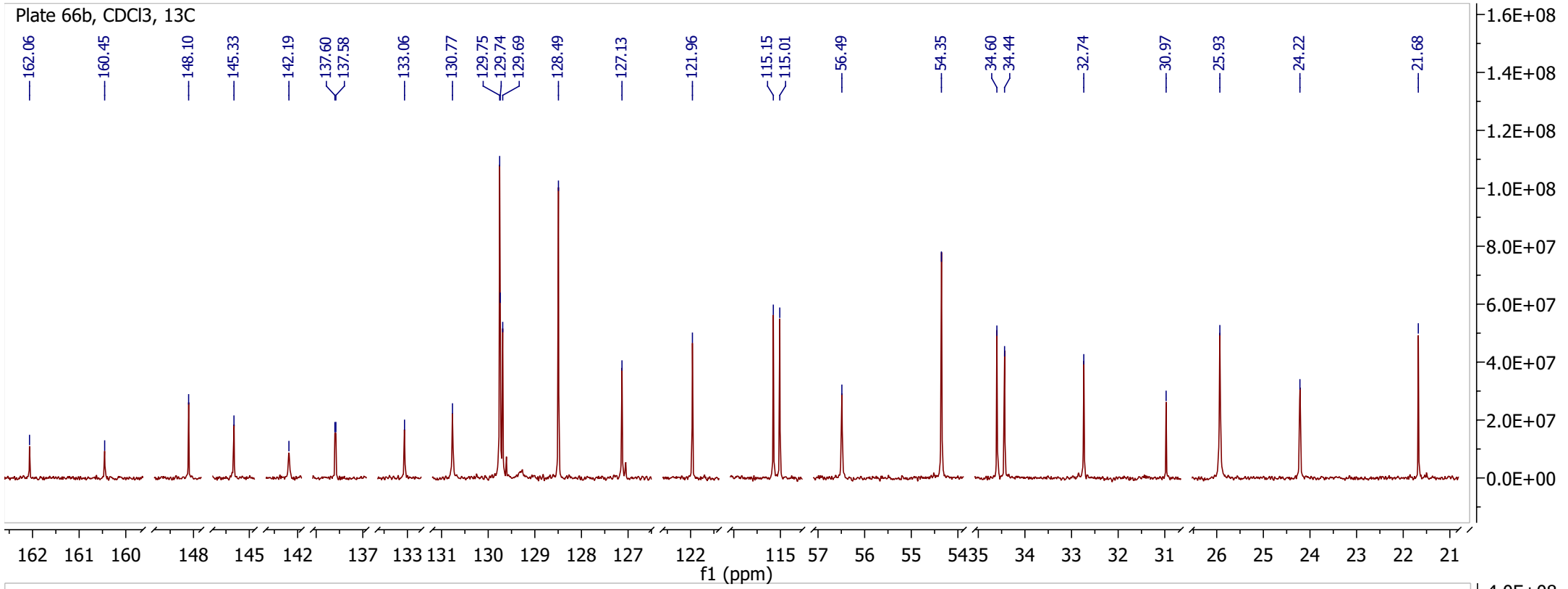
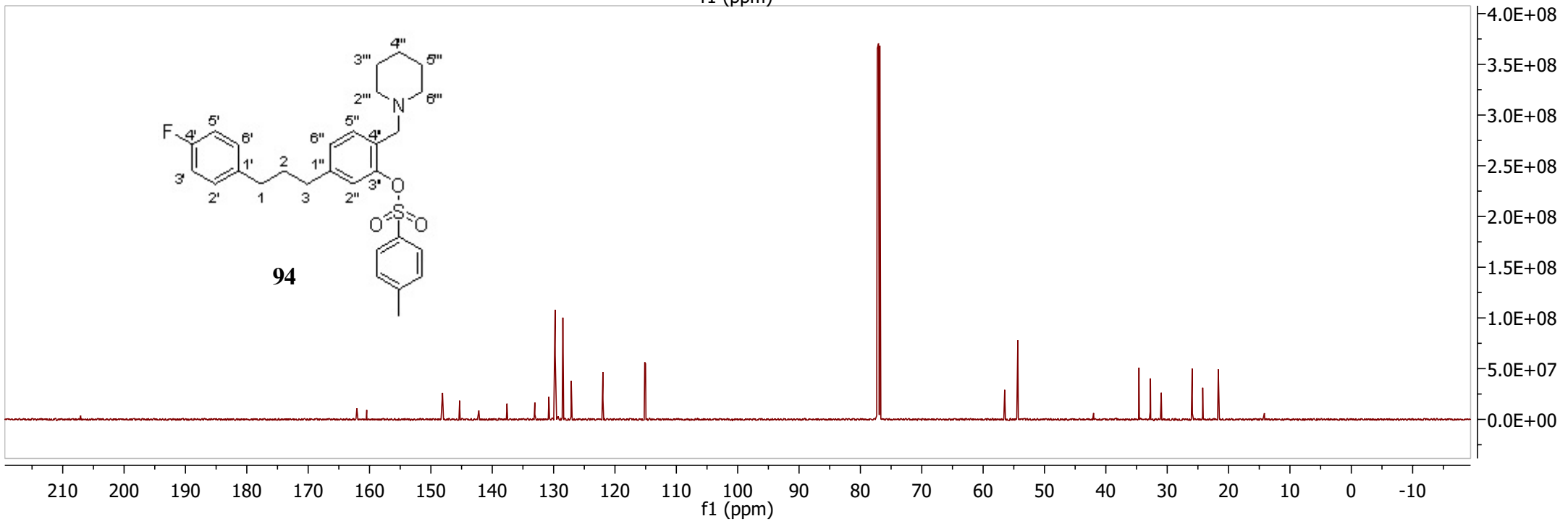


Plate 66b, CDCl3, 13C
162.06
160.45
148.10
145.33
142.19
137.60
137.58
133.06
130.77
129.75
129.74
129.69
128.49
127.13
121.96
115.15
115.01
56.49
54.35
34.60
34.44
32.74
30.97
25.93
24.22
21.68
f1 (ppm)


94
f1 (ppm)

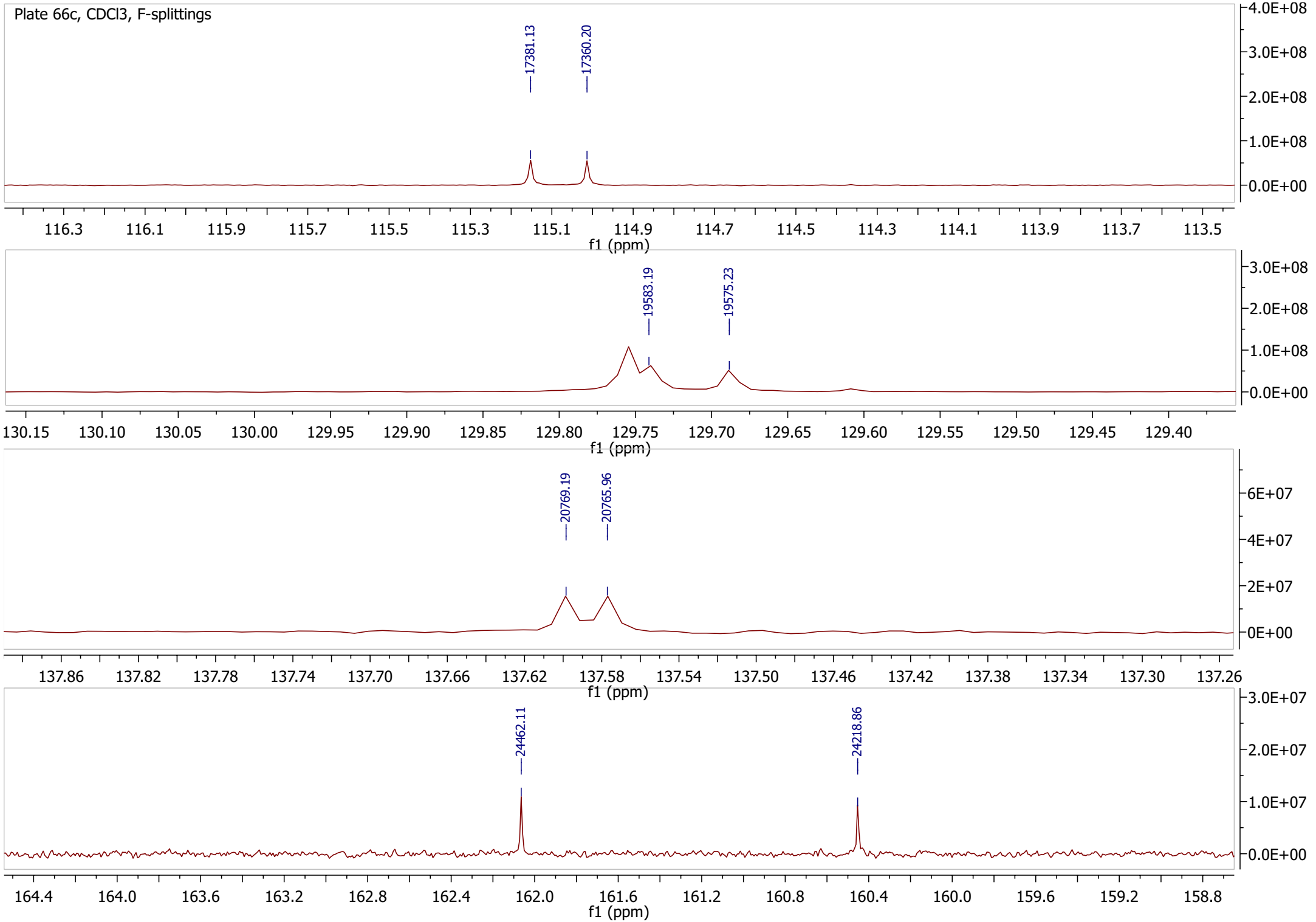


Plate 66c, CDCl3, F-splittings
17381.13
17360.20
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
116.3 116.1 115.9 115.7 115.5 115.3 115.1 114.9 114.7 114.5 114.3 114.1 113.9 113.7 113.5
f1 (ppm)
19583.19
19575.23
3.0E+08
2.0E+08
1.0E+08
0.0E+00
130.15 130.10 130.05 130.00 129.95 129.90 129.85 129.80 129.75 129.70 129.65 129.60 129.55 129.50 129.45 129.40
f1 (ppm)
20769.19
20765.96
6E+07
4E+07
2E+07
0E+00
137.86 137.82 137.78 137.74 137.70 137.66 137.62 137.58 137.54 137.50 137.46 137.42 137.38 137.34 137.30 137.26
f1 (ppm)
24462.11
24218.86
3.0E+07
2.0E+07
1.0E+07
0.0E+00
164.4 164.0 163.6 163.2 162.8 162.4 162.0 161.6 161.2 160.8 160.4 160.0 159.6 159.2 158.8
f1 (ppm)

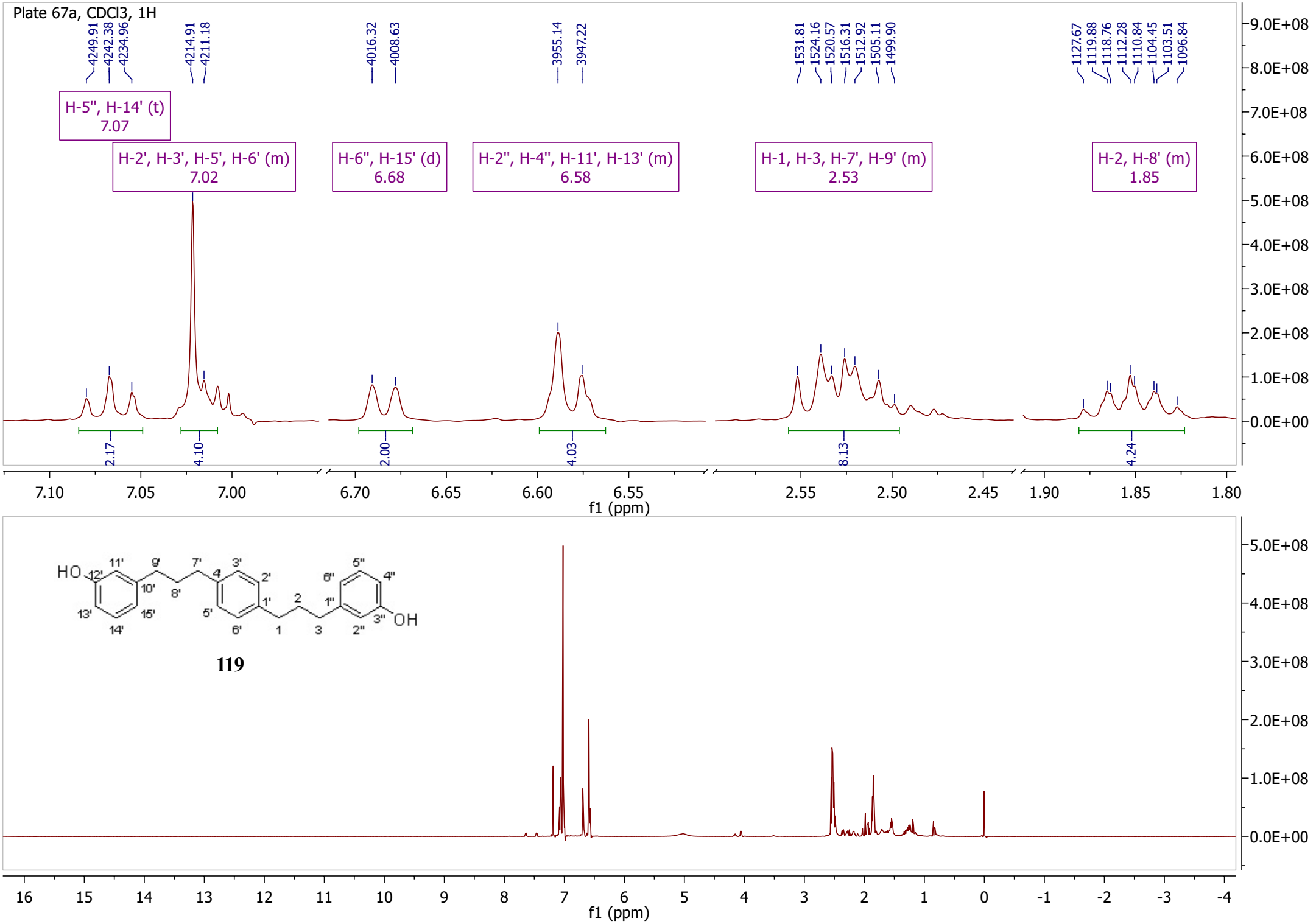
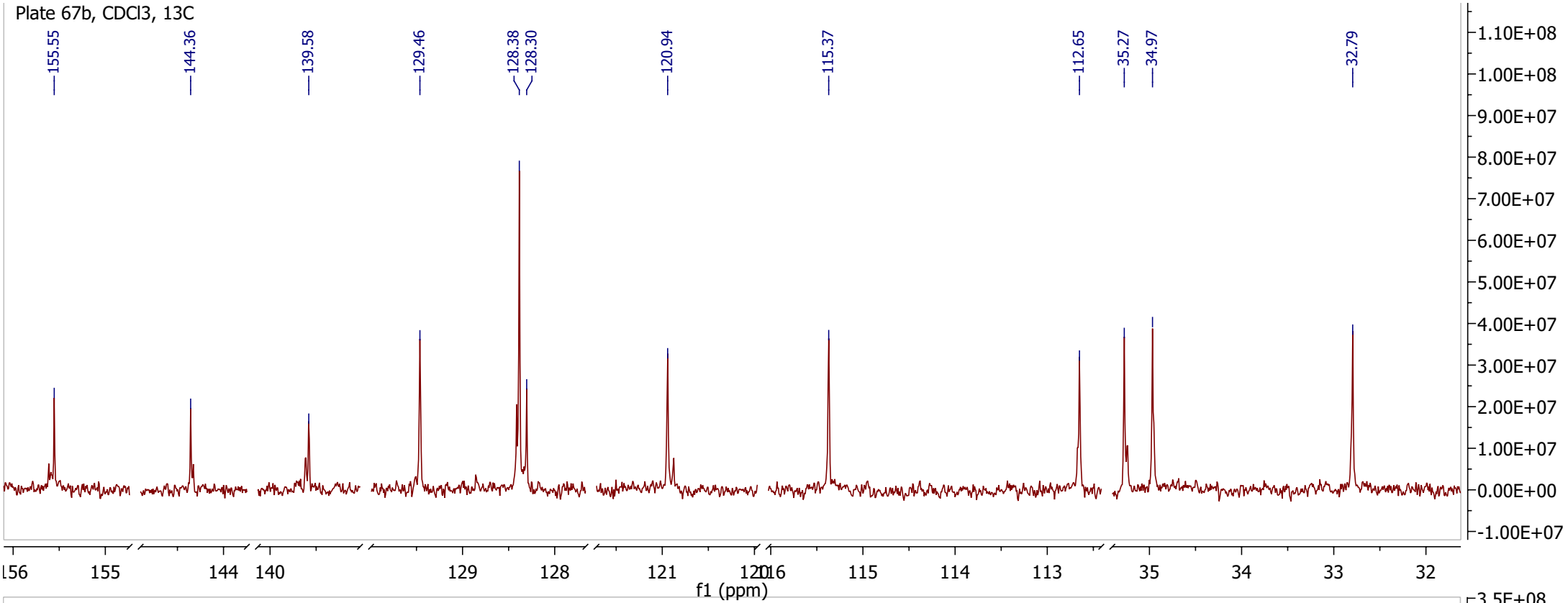
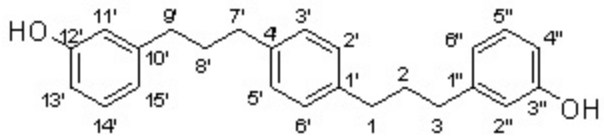


Plate 67a, CDCl3, 1H
4249.91
4242.38
4234.96
4214.91
4211.18
4016.32
4008.63
3955.14
3947.22
1531.81
1524.16
1520.57
1516.31
1512.92
1505.11
1499.90
1127.67
1119.88
1118.76
1112.28
1110.84
1104.45
1103.51
1096.84
H-5'', H-14' (t)
7.07
H-2', H-3', H-5', H-6' (m)
7.02
H-6'', H-15' (d)
6.68
H-2'', H-4'', H-11', H-13' (m)
6.58
H-1, H-3, H-7', H-9' (m)
2.53
H-2, H-8' (m)
1.85
2.17
4.10
2.00
4.03
8.13
4.24
f1 (ppm)
HO
OH
119
f1 (ppm)

Plate 67b, CDCl3, 13C





119

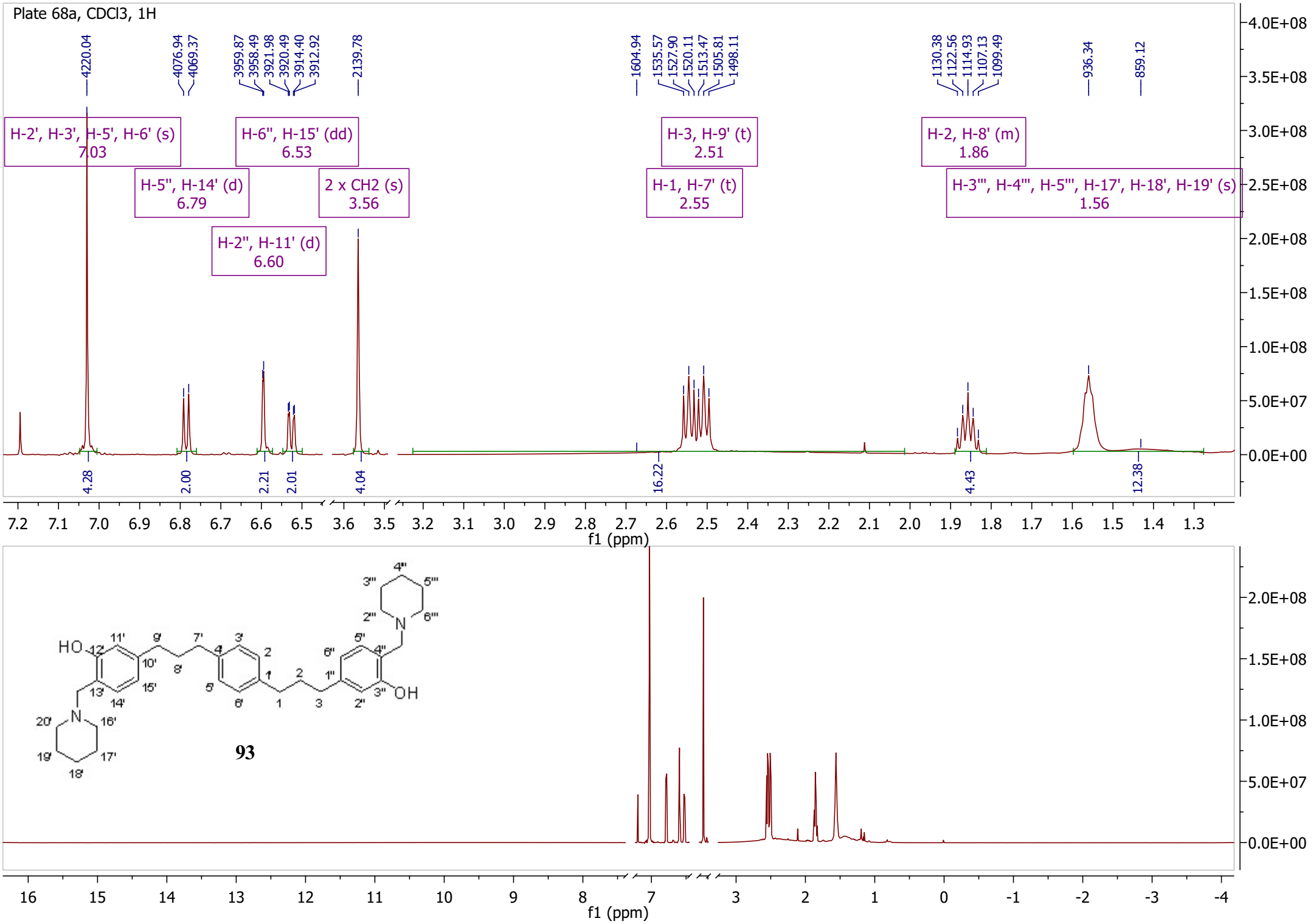


Plate 68a, CDCl3, 1H
4220.04
4076.94
4069.37
3959.87
3958.49
3921.98
3920.49
3914.40
3912.92
2139.78
1604.94
1535.57
1527.90
1520.11
1513.47
1505.81
1498.11
1130.38
1122.56
1114.93
1107.13
1099.49
936.34
859.12
H-2', H-3', H-5', H-6' (s)
7.03
H-5", H-14' (d)
6.79
H-6", H-15' (dd)
6.53
H-2", H-11' (d)
6.60
2 x CH2 (s)
3.56
H-3, H-9' (t)
2.51
H-1, H-7' (t)
2.55
H-2, H-8' (m)
1.86
H-3"', H-4"', H-5"', H-17', H-18', H-19' (s)
1.56
4.28
2.00
2.21
2.01
4.04
16.22
4.43
12.38
f1 (ppm)
HO
OH
N
93
f1 (ppm)

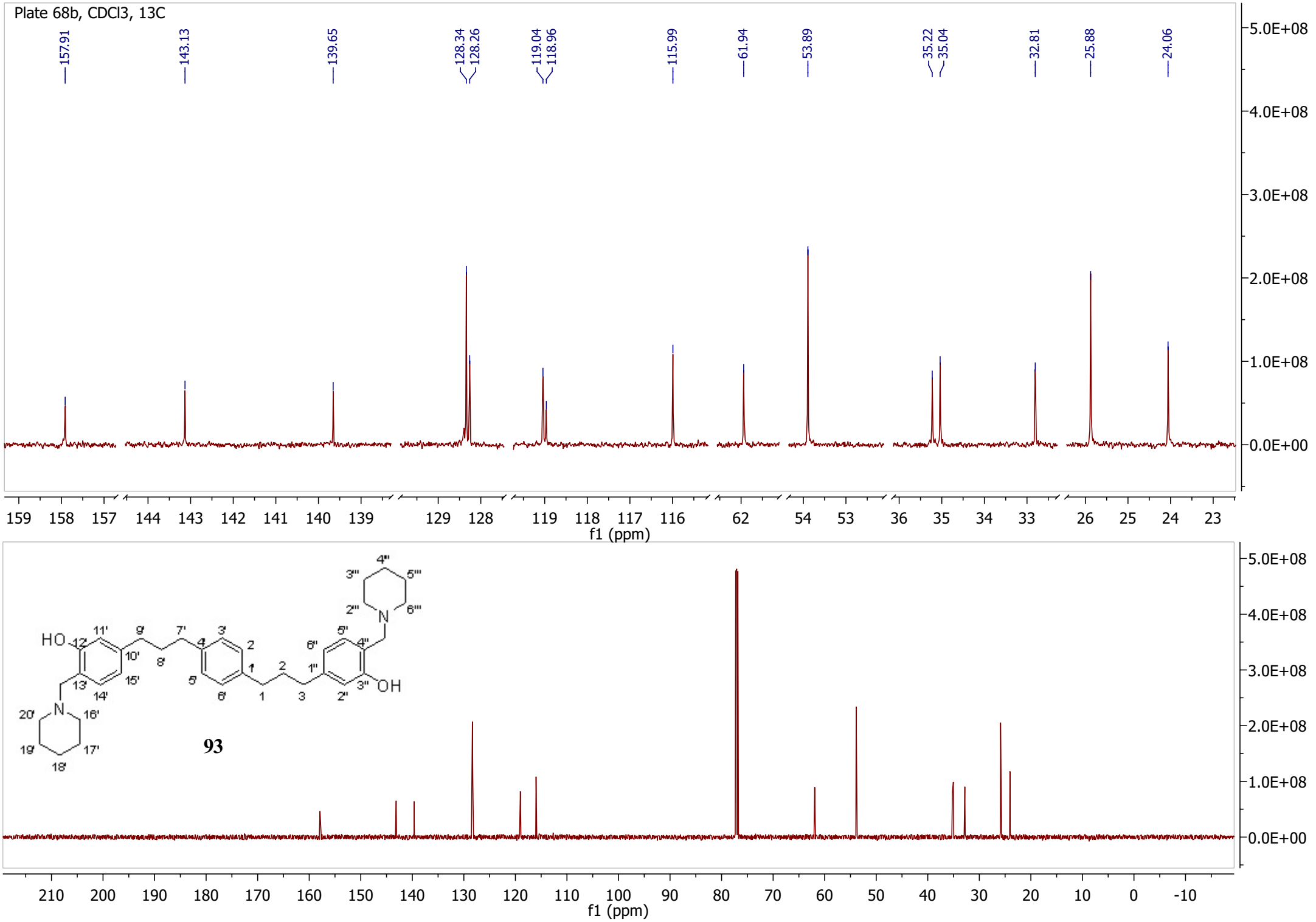


Plate 68b, CDCl3, 13C
157.91
143.13
139.65
128.34
128.26
119.04
118.96
115.99
61.94
53.89
35.22
35.04
32.81
25.88
24.06
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
159 158 157 144 143 142 141 140 139 129 128 119 118 117 116 62 54 53 36 35 34 33 26 25 24 23
f1 (ppm)
HO
OH
N
93
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

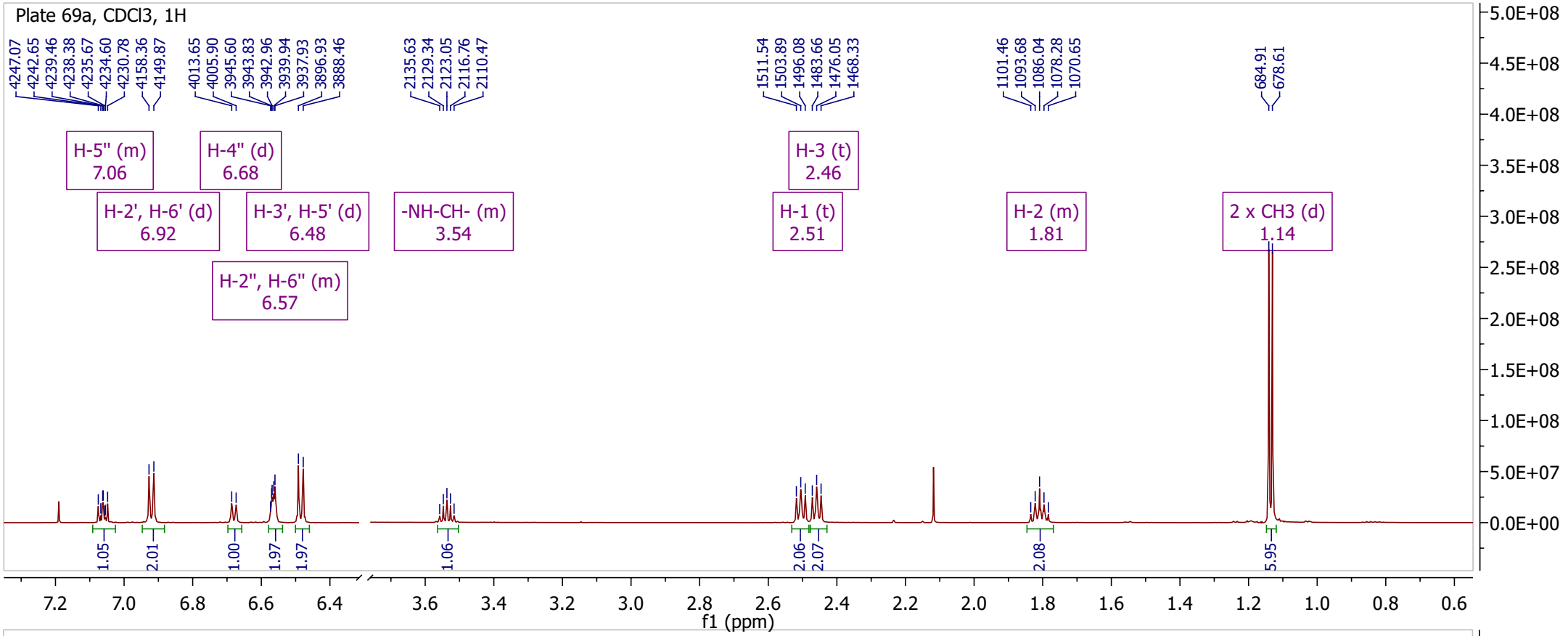
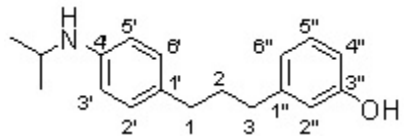


Plate 69a, CDCl3, 1H
4247.07
4242.65
4239.46
4238.38
4235.67
4234.60
4230.78
4158.36
4149.87
4013.65
4005.90
3945.60
3943.83
3942.96
3939.94
3937.93
3896.93
3888.46
2135.63
2129.34
2123.05
2116.76
2110.47
1511.54
1503.89
1496.08
1483.66
1476.05
1468.33
1101.46
1093.68
1086.04
1078.28
1070.65
684.91
678.61
H-5" (m)
7.06
H-4" (d)
6.68
H-3 (t)
2.46
H-2', H-6' (d)
6.92
H-3', H-5' (d)
6.48
-NH-CH- (m)
3.54
H-1 (t)
2.51
H-2 (m)
1.81
2 x CH3 (d)
1.14
H-2", H-6" (m)
6.57
1.05
2.01
1.00
1.97
1.97
1.06
2.06
2.07
2.08
5.95
f1 (ppm)


H
N
5'
4'
6'
1'
2
6"
5"
4"
3"
3'
2'
1
3
1"
2"
OH

92

f1 (ppm)

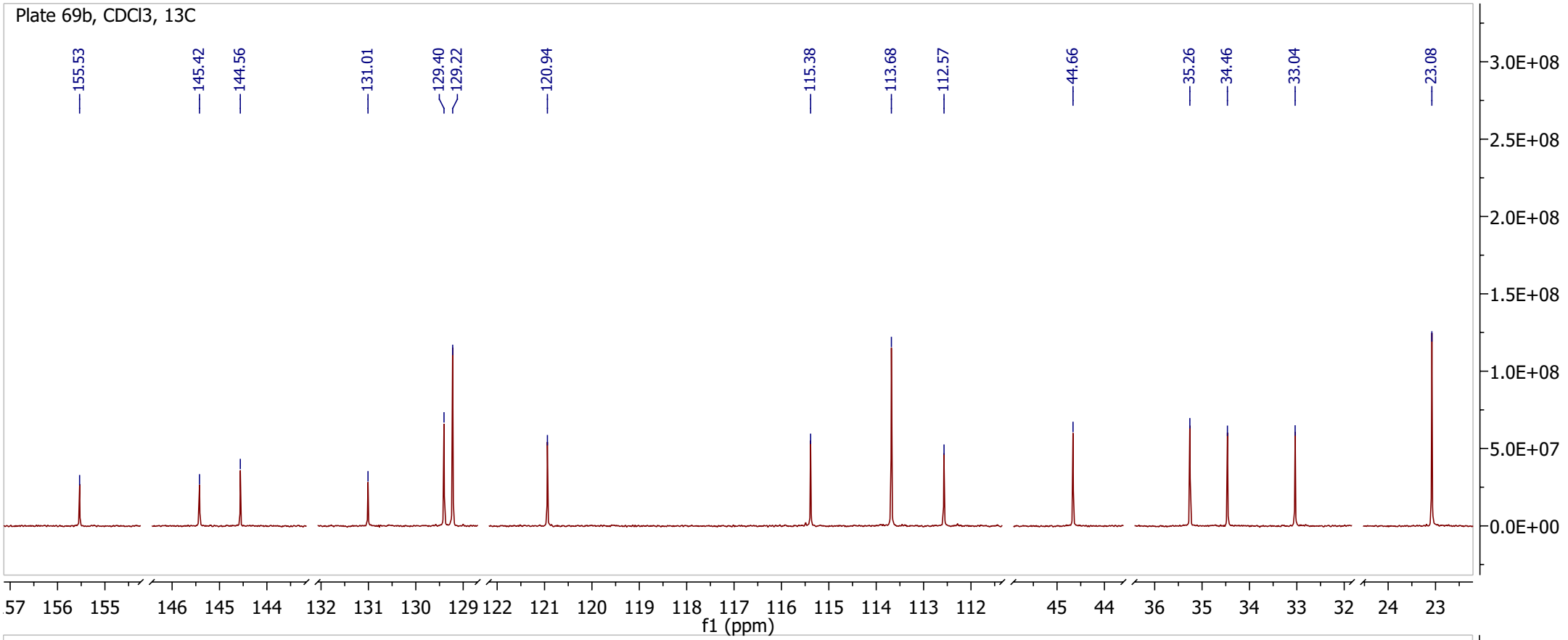
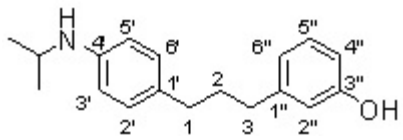


Plate 69b, CDCl3, 13C
155.53
145.42
144.56
131.01
129.40
129.22
120.94
115.38
113.68
112.57
44.66
35.26
34.46
33.04
23.08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
57 156 155 146 145 144 132 131 130 129 122 121 120 119 118 117 116 115 114 113 112 45 44 36 35 34 33 32 24 23
f1 (ppm)


NH
OH

92

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

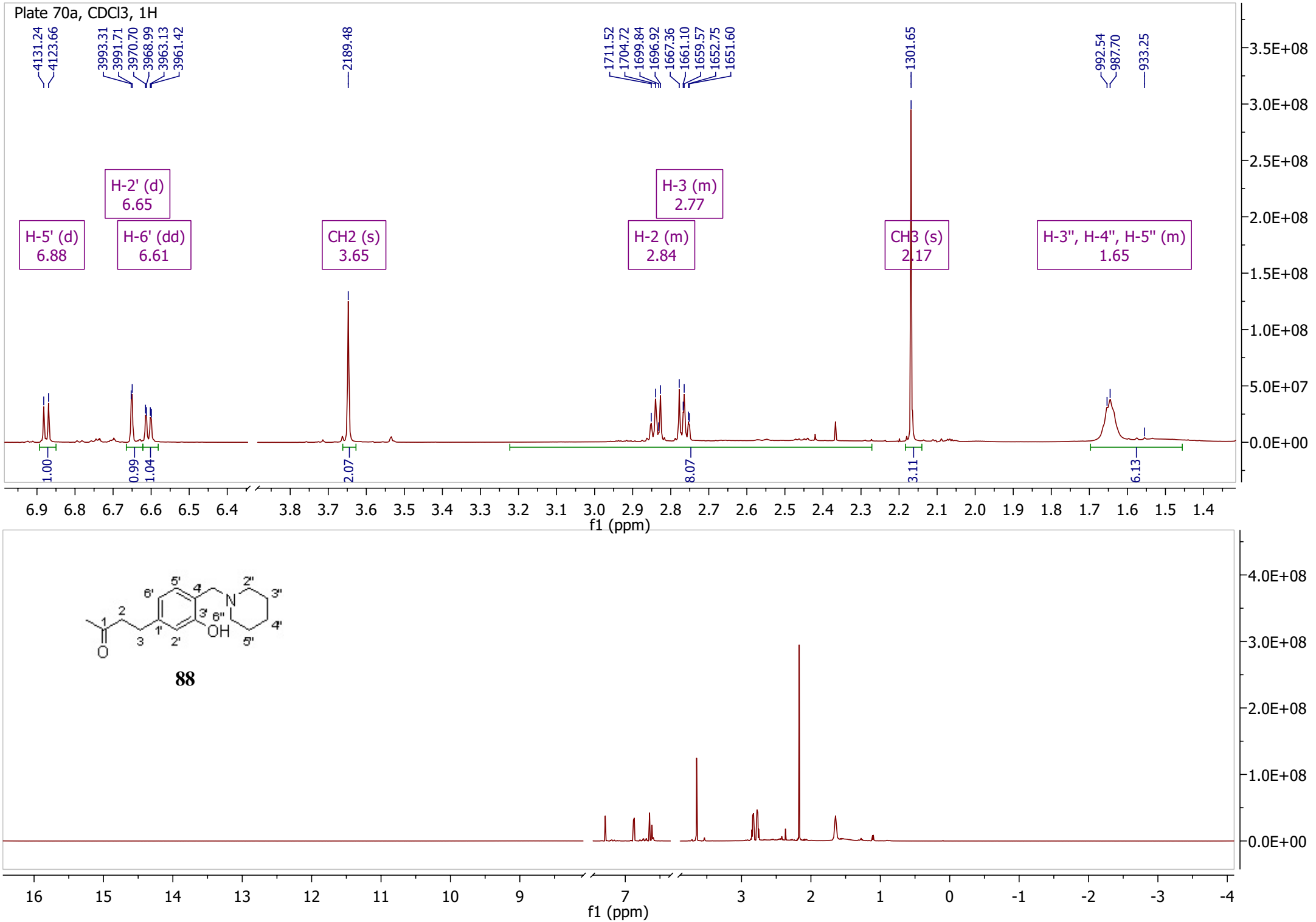


Plate 70a, CDCl3, 1H
4131.24
4123.66
3993.31
3991.71
3970.70
3968.99
3963.13
3961.42
2189.48
1711.52
1704.72
1699.84
1696.92
1667.36
1661.10
1659.57
1652.75
1651.60
1301.65
992.54
987.70
933.25
H-5' (d)
6.88
H-2' (d)
6.65
H-6' (dd)
6.61
CH2 (s)
3.65
H-3 (m)
2.77
H-2 (m)
2.84
CH3 (s)
2.17
H-3", H-4", H-5" (m)
1.65
1.00
0.99
1.04
2.07
8.07
3.11
6.13
f1 (ppm)
88
f1 (ppm)

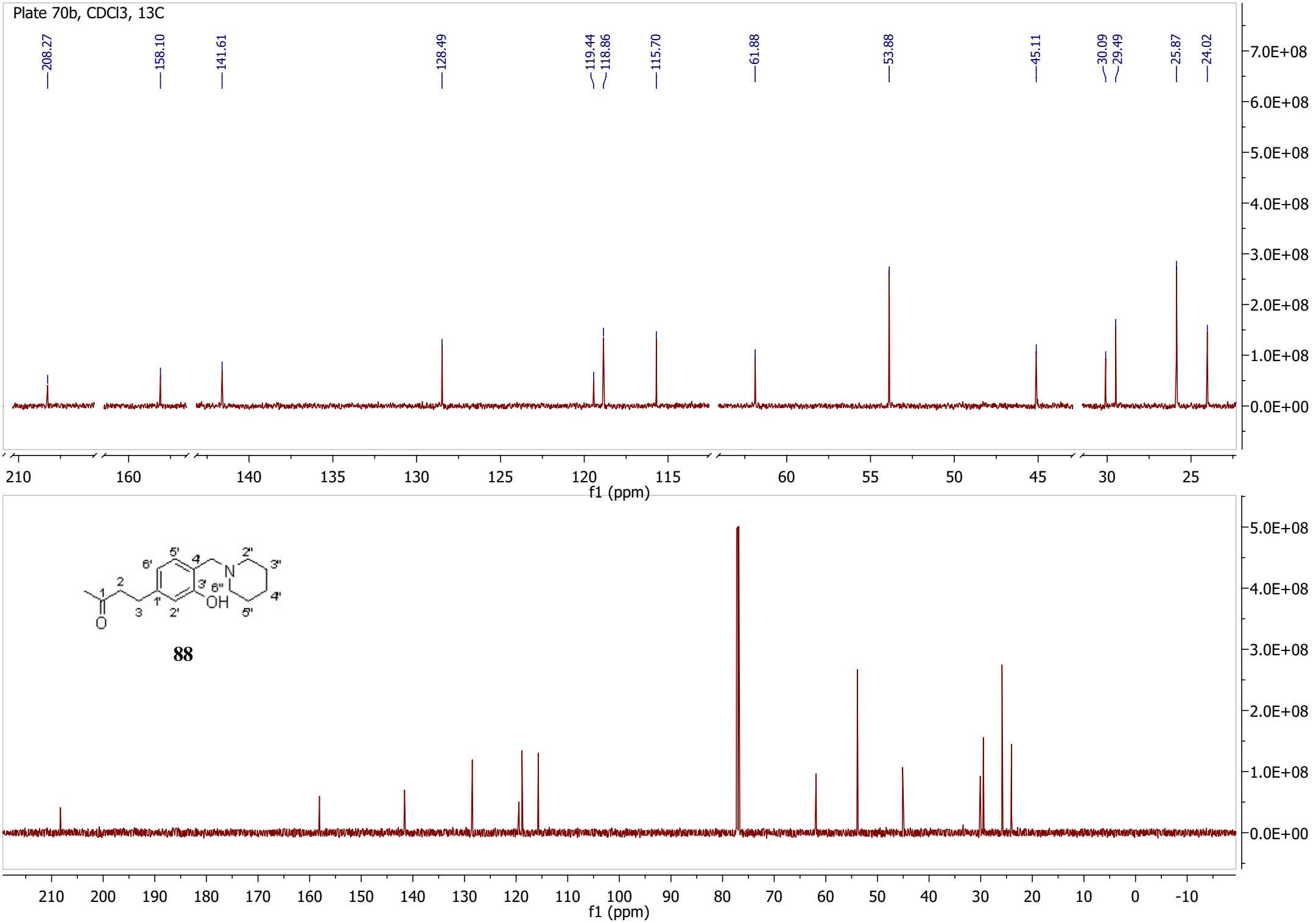


Plate 70b, CDCl3, 13C
208.27
158.10
141.61
128.49
119.44
118.86
115.70
61.88
53.88
45.11
30.09
29.49
25.87
24.02
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210
160
140
135
130
125
120
115
60
55
50
45
30
25
f1 (ppm)
88
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

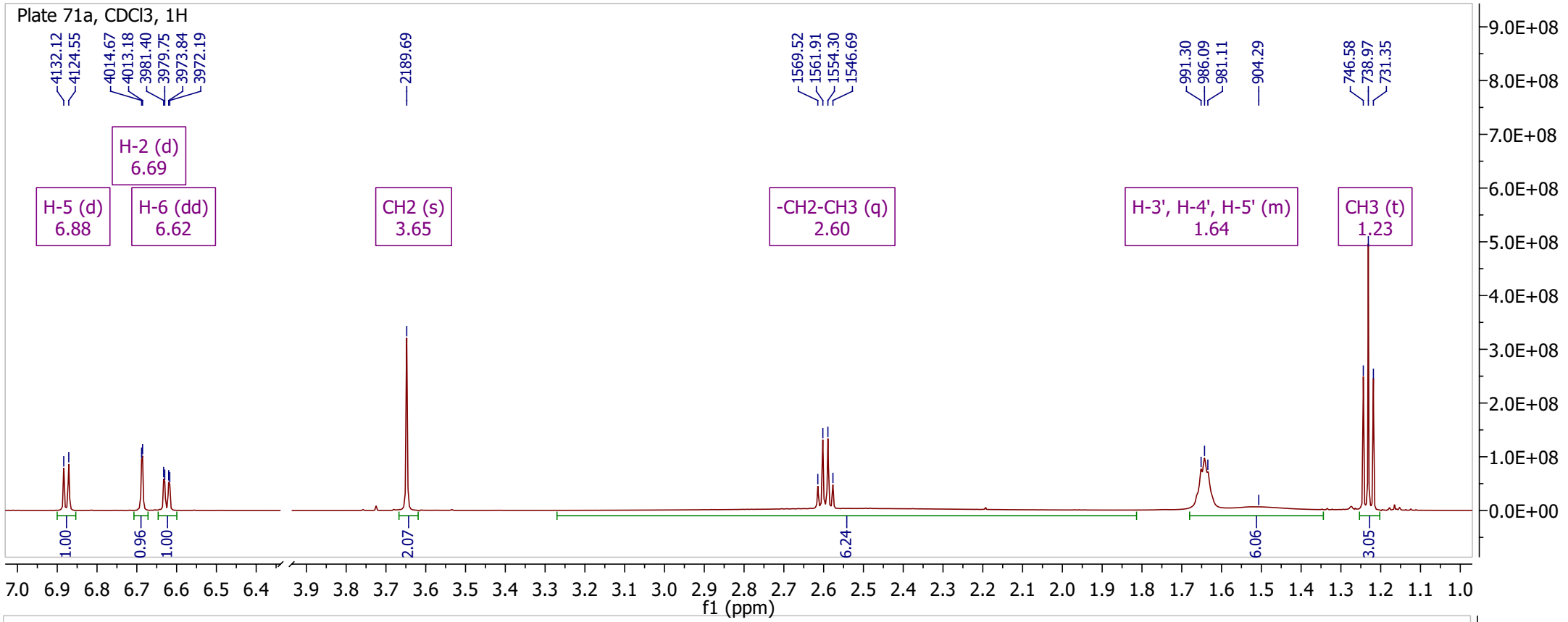
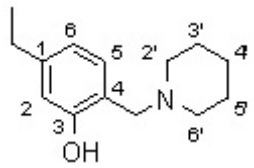


Plate 71a, CDCl3, 1H
4132.12
4124.55
4014.67
4013.18
3981.40
3979.75
3973.84
3972.19
2189.69
1569.52
1561.91
1554.30
1546.69
991.30
986.09
981.11
904.29
746.58
738.97
731.35
H-2 (d)
6.69
H-5 (d)
6.88
H-6 (dd)
6.62
CH2 (s)
3.65
-CH2-CH3 (q)
2.60
H-3', H-4', H-5' (m)
1.64
CH3 (t)
1.23
1.00
0.96
1.00
2.07
6.24
6.06
3.05
f1 (ppm)


OH
N

87

f1 (ppm)

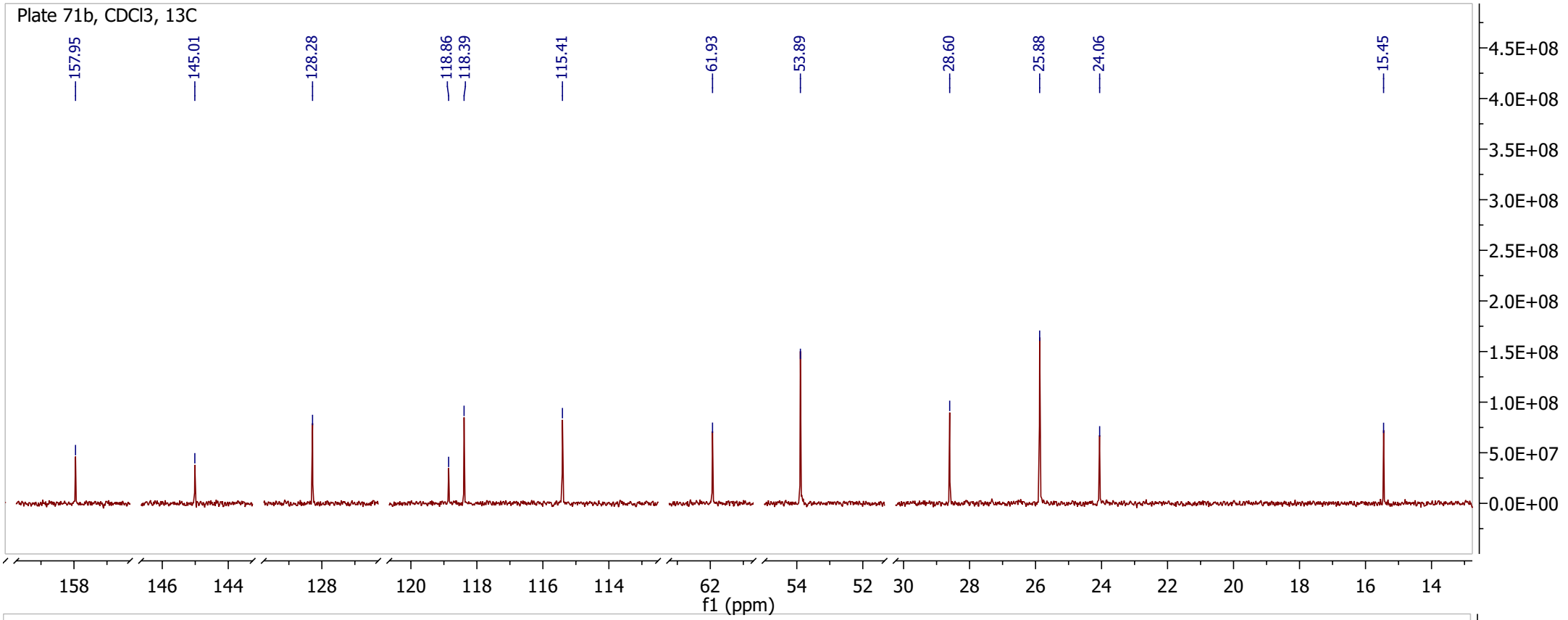
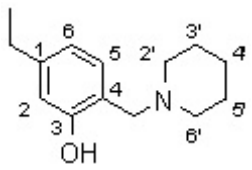


Plate 71b, CDCl3, 13C
157.95
145.01
128.28
118.86
118.39
115.41
61.93
53.89
28.60
25.88
24.06
15.45
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
158
146
144
128
120
118
116
114
62
54
52
30
28
26
24
22
20
18
16
14
f1 (ppm)


1
2
3
OH
4
5
6
2'
N
3'
4'
5'
6'

87

4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

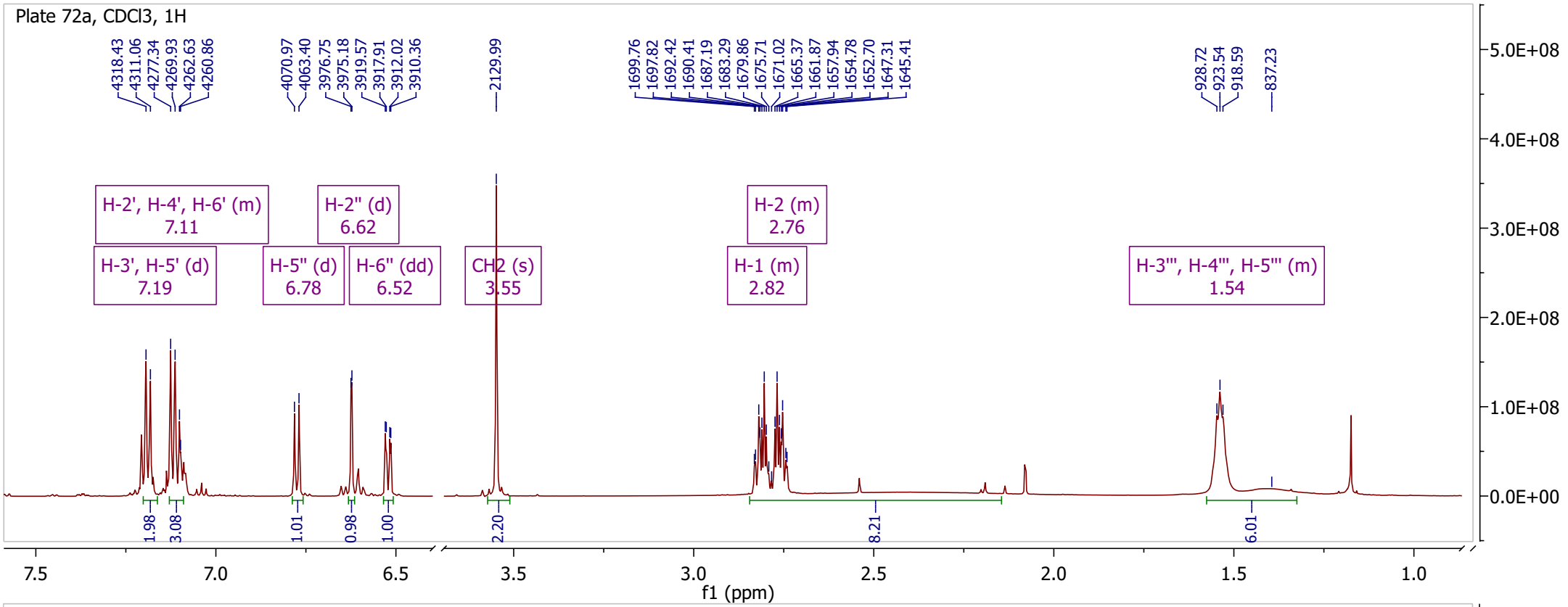
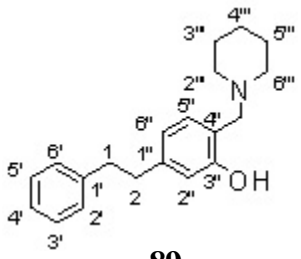


Plate 72a, CDCl3, 1H
4318.43
4311.06
4277.34
4269.93
4262.63
4260.86
4070.97
4063.40
3976.75
3975.18
3919.57
3917.91
3912.02
3910.36
2129.99
1699.76
1697.82
1692.42
1690.41
1687.19
1683.29
1679.86
1675.71
1671.02
1665.37
1661.87
1657.94
1654.78
1652.70
1647.31
1645.41
928.72
923.54
918.59
837.23
H-2', H-4', H-6' (m)
7.11
H-2" (d)
6.62
H-2 (m)
2.76
H-3', H-5' (d)
7.19
H-5" (d)
6.78
H-6" (dd)
6.52
CH2 (s)
3.55
H-1 (m)
2.82
H-3"', H-4"', H-5"' (m)
1.54
1.98
3.08
1.01
0.98
1.00
2.20
8.21
6.01
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
7.5
7.0
6.5
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


4'''
3''
5'''
2''
N
6'''
5'
4'
6''
6'
1
1''
5'
1'
2
2''
3''
OH
4'
2'
3'

89

3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

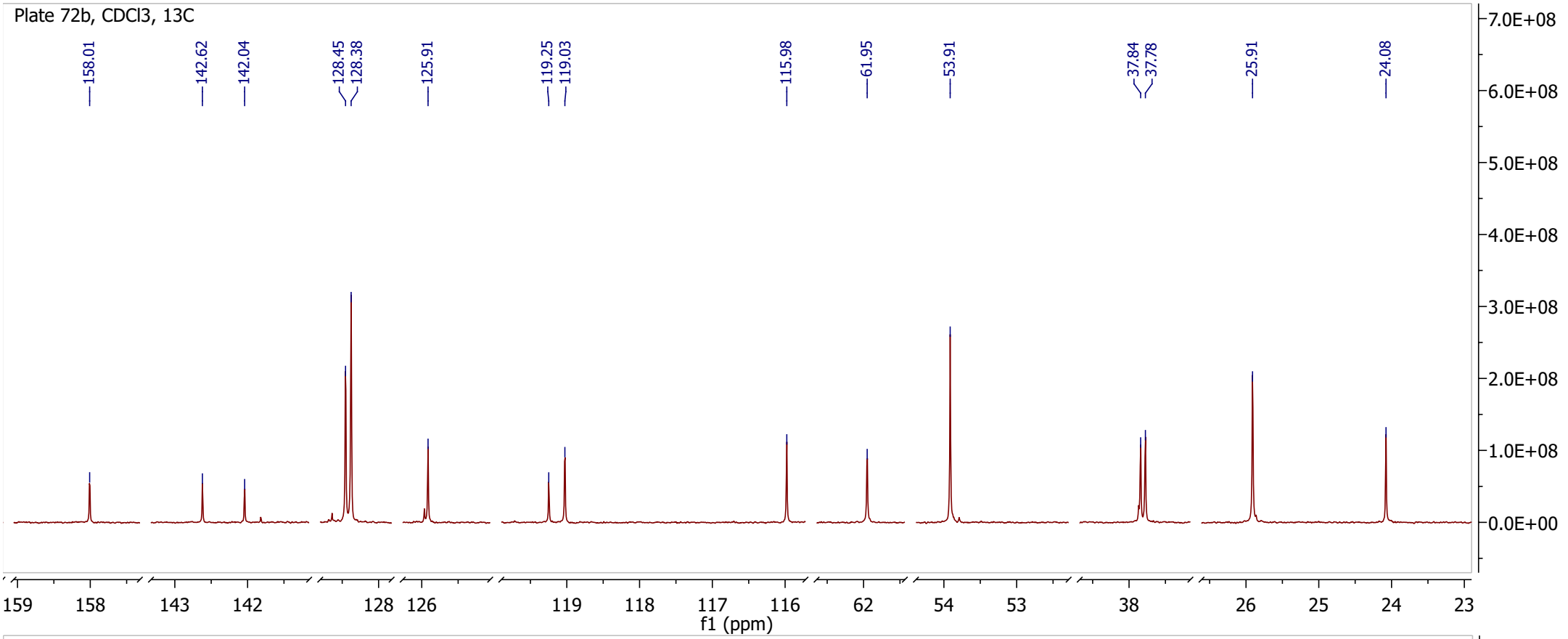
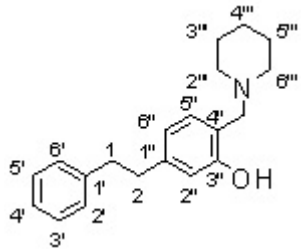


Plate 72b, CDCl3, 13C
158.01
142.62
142.04
128.45
128.38
125.91
119.25
119.03
115.98
61.95
53.91
37.84
37.78
25.91
24.08
7.0E+08
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
159
158
143
142
128
126
119
118
117
116
62
54
53
38
26
25
24
23
f1 (ppm)


4'''
3''
5'''
2''
N
6'''
5'
4'
6''
6'
1
1''
5'
1'
2
2''
3''
OH
4'
2'
3'

89

3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

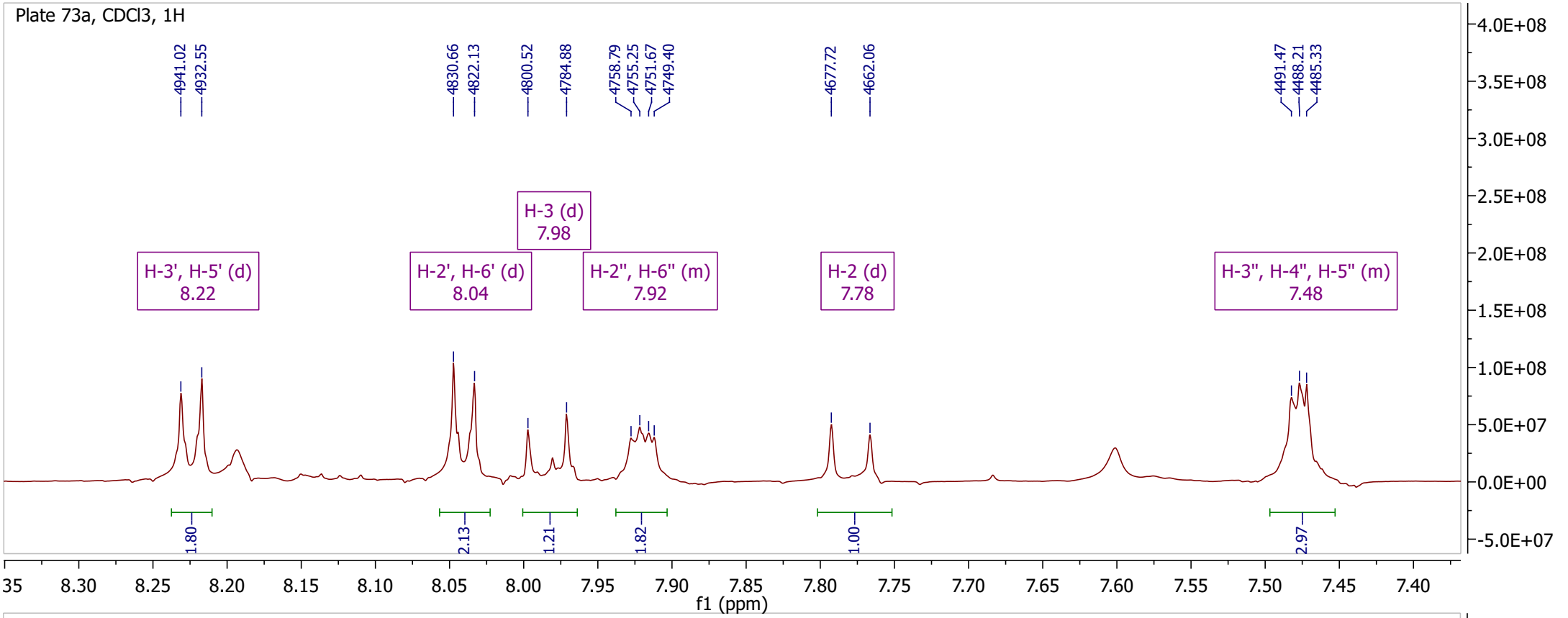
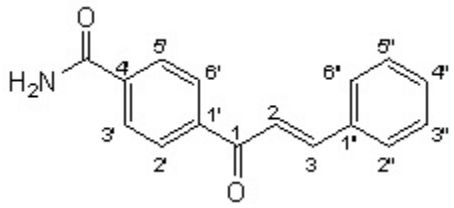


Plate 73a, CDCl3, 1H
4941.02
4932.55
4830.66
4822.13
4800.52
4784.88
4758.79
4755.25
4751.67
4749.40
4677.72
4662.06
4491.47
4488.21
4485.33
H-3 (d)
7.98
H-3', H-5' (d)
8.22
H-2', H-6' (d)
8.04
H-2", H-6" (m)
7.92
H-2 (d)
7.78
H-3", H-4", H-5" (m)
7.48
1.80
2.13
1.21
1.82
1.00
2.97
f1 (ppm)


O
H2N
O

120

f1 (ppm)

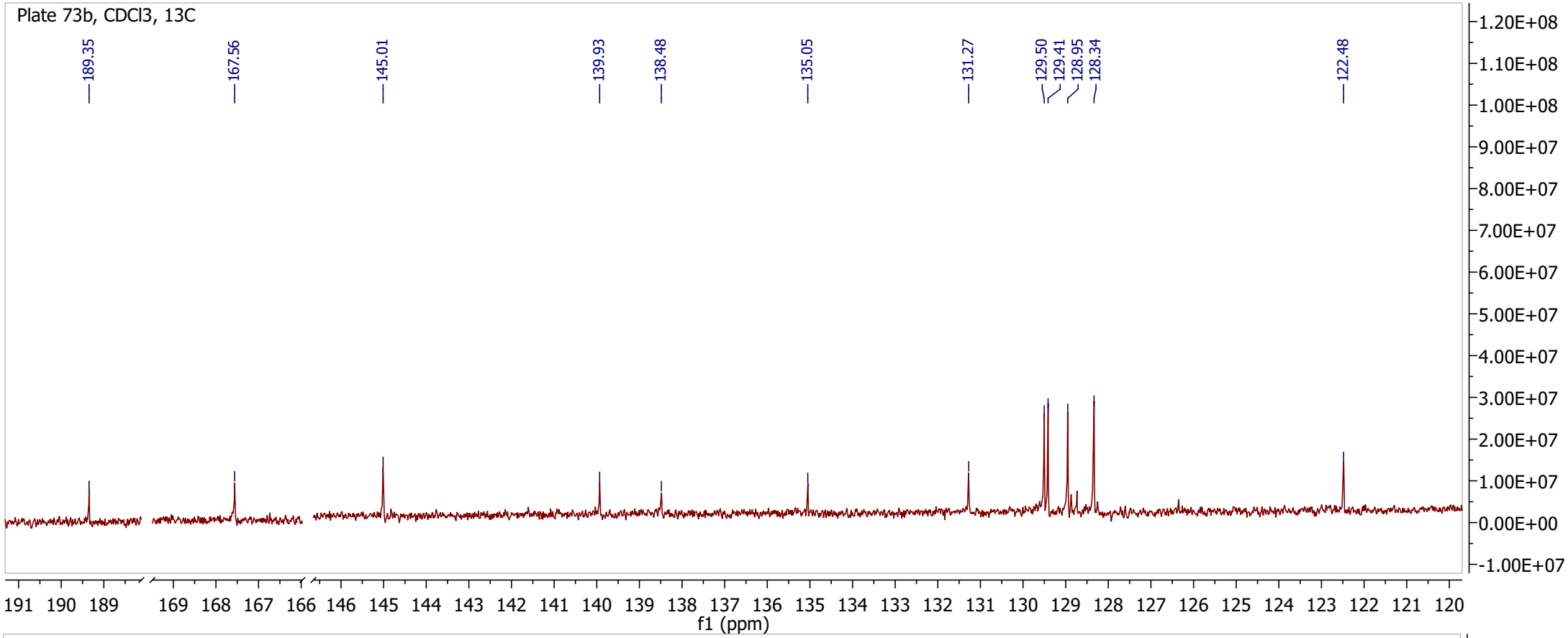
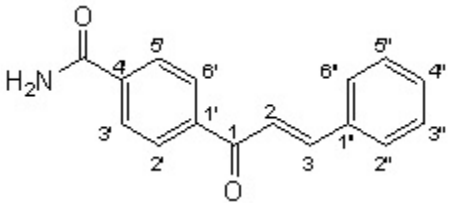


Plate 73b, CDCl3, 13C
189.35
167.56
145.01
139.93
138.48
135.05
131.27
129.50
129.41
128.95
128.34
122.48
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
191 190 189 169 168 167 166 146 145 144 143 142 141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120
f1 (ppm)


O
H2N
4
5
6'
1'
2
3'
1
2'
3
O
5'
6'
4'
1''
3''
2''

120

3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

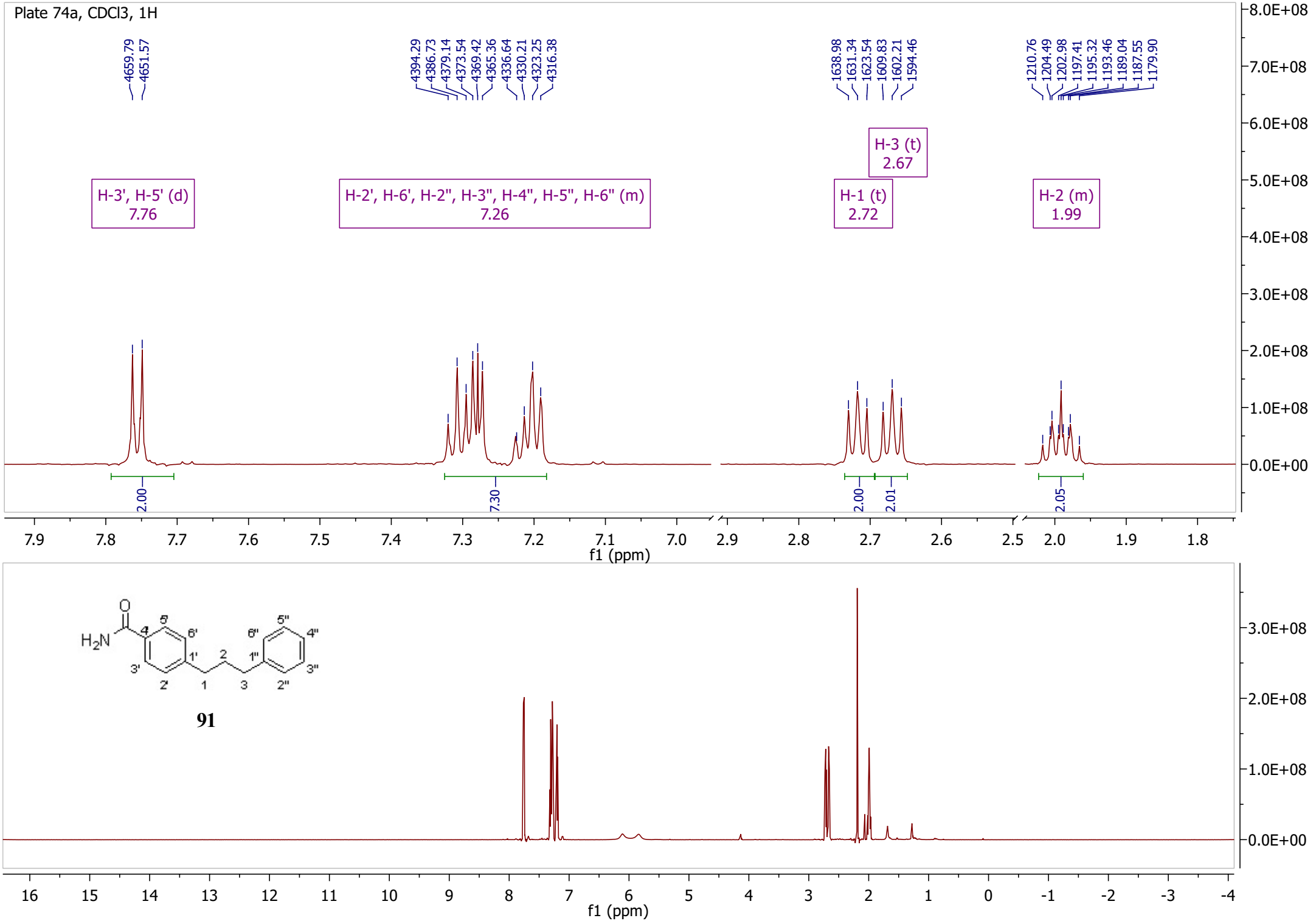


Plate 74a, CDCl3, 1H
4659.79
4651.57
4394.29
4386.73
4379.14
4373.54
4369.42
4365.36
4336.64
4330.21
4323.25
4316.38
1638.98
1631.34
1623.54
1609.83
1602.21
1594.46
1210.76
1204.49
1202.98
1197.41
1195.32
1193.46
1189.04
1187.55
1179.90
H-3', H-5' (d)
7.76
H-2', H-6', H-2", H-3", H-4", H-5", H-6" (m)
7.26
H-3 (t)
2.67
H-1 (t)
2.72
H-2 (m)
1.99
2.00
7.30
2.00
2.01
2.05
f1 (ppm)
f1 (ppm)

91

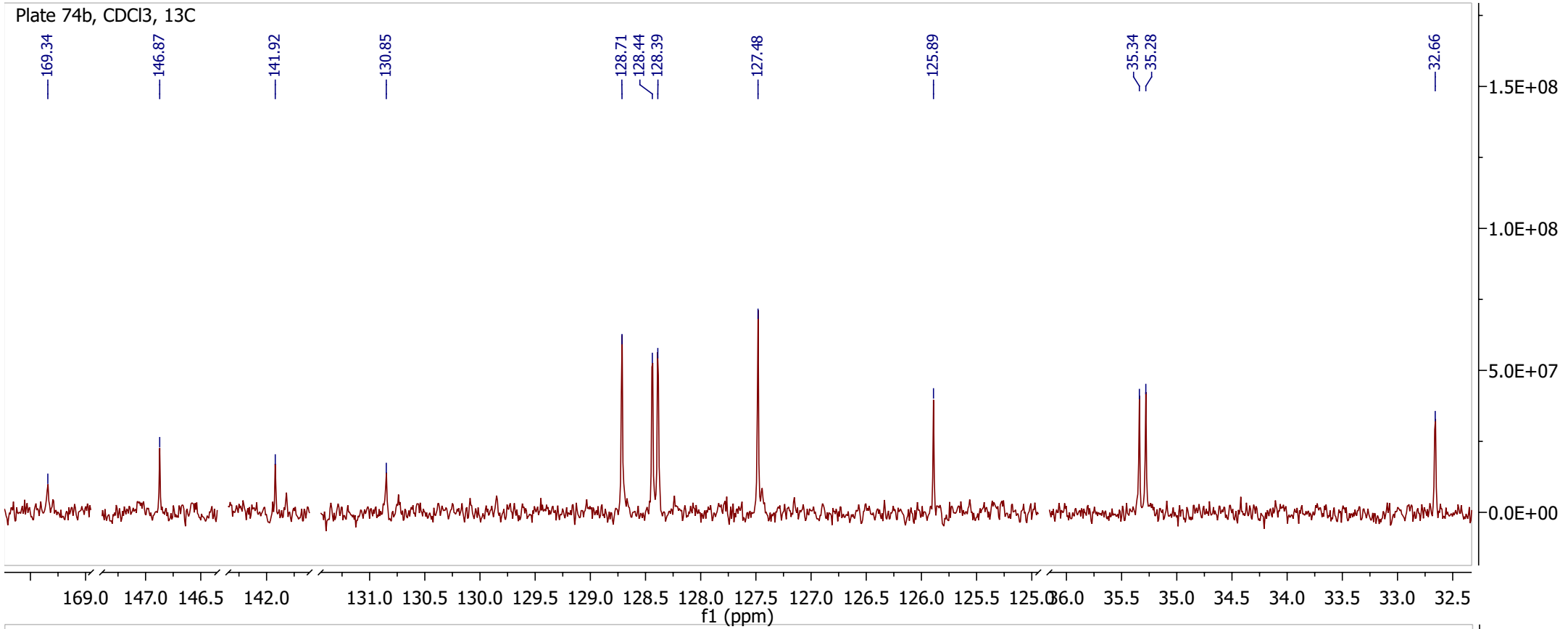
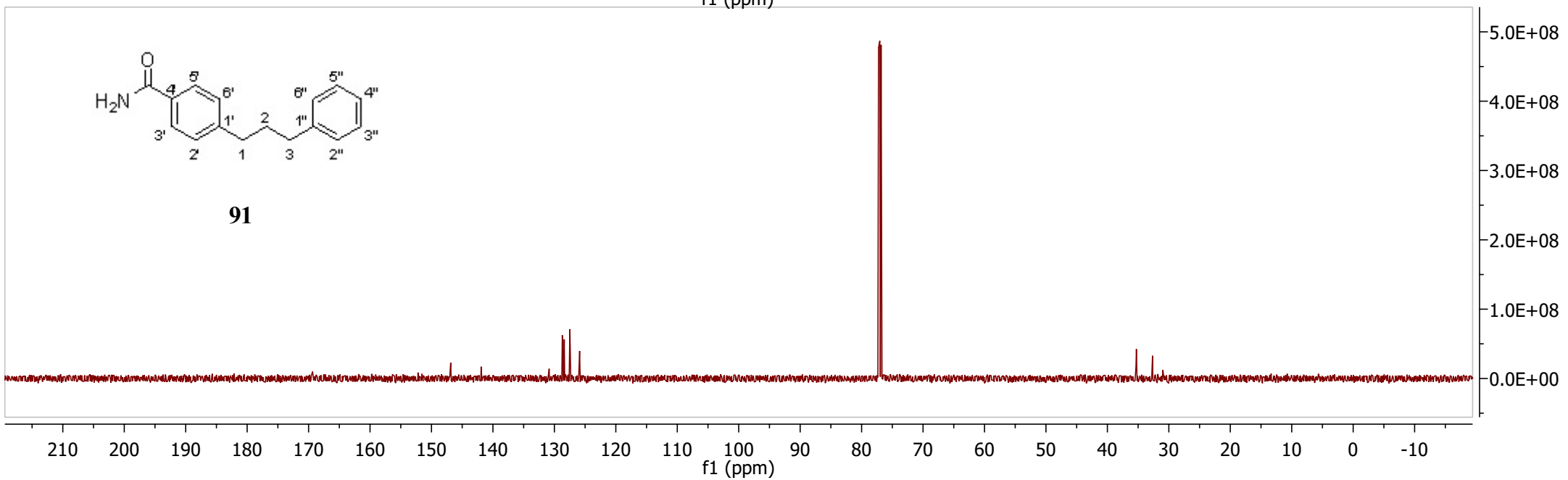


Plate 74b, CDCl3, 13C
169.34
146.87
141.92
130.85
128.71
128.44
128.39
127.48
125.89
35.34
35.28
32.66
1.5E+08
1.0E+08
5.0E+07
0.0E+00
169.0 147.0 146.5 142.0 131.0 130.5 130.0 129.5 129.0 128.5 128.0 127.5 127.0 126.5 126.0 125.5 125.0 36.0 35.5 35.0 34.5 34.0 33.5 33.0 32.5
f1 (ppm)


5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

O
H2N
4
5'
6'
1'
2
3'
2'
1
3
1"
6"
5"
4"
3"
2"

91

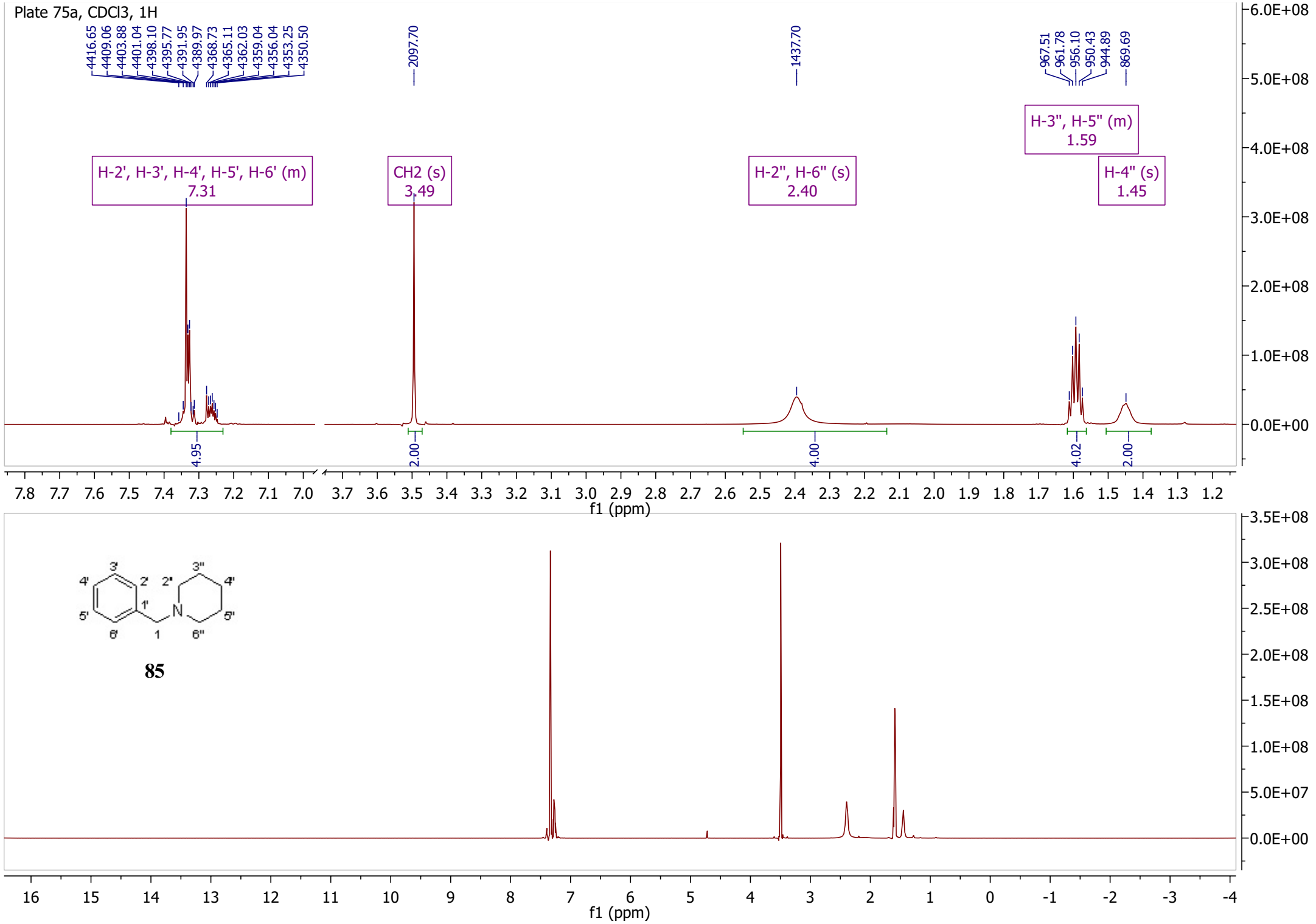


Plate 75a, CDCl3, 1H
4416.65
4409.06
4403.88
4401.04
4398.10
4395.77
4391.95
4389.97
4368.73
4365.11
4362.03
4359.04
4356.04
4353.25
4350.50
2097.70
1437.70
967.51
961.78
956.10
950.43
944.89
869.69
H-2', H-3', H-4', H-5', H-6' (m)
7.31
CH2 (s)
3.49
H-2", H-6" (s)
2.40
H-3", H-5" (m)
1.59
H-4" (s)
1.45
4.95
2.00
4.00
4.02
2.00
f1 (ppm)
f1 (ppm)
3'
4'
2'
1'
5'
6'
1
2"
3"
4'
5'
6"
N
85

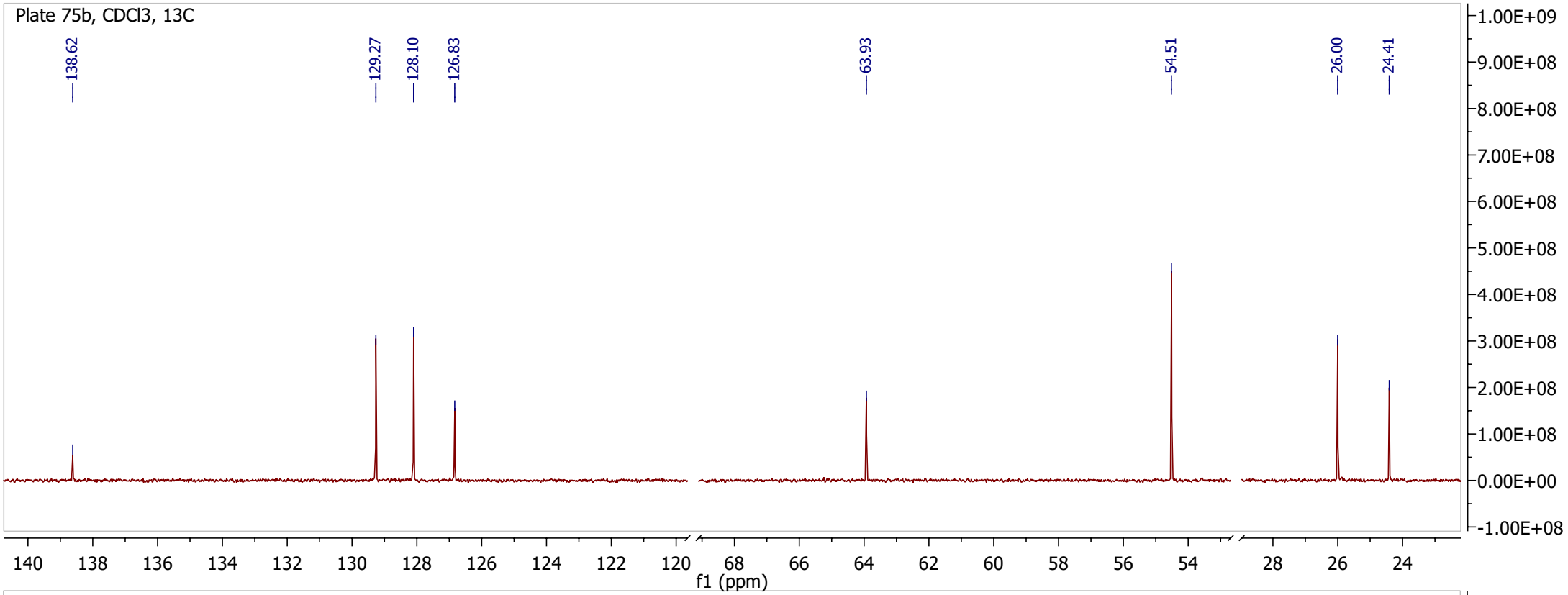
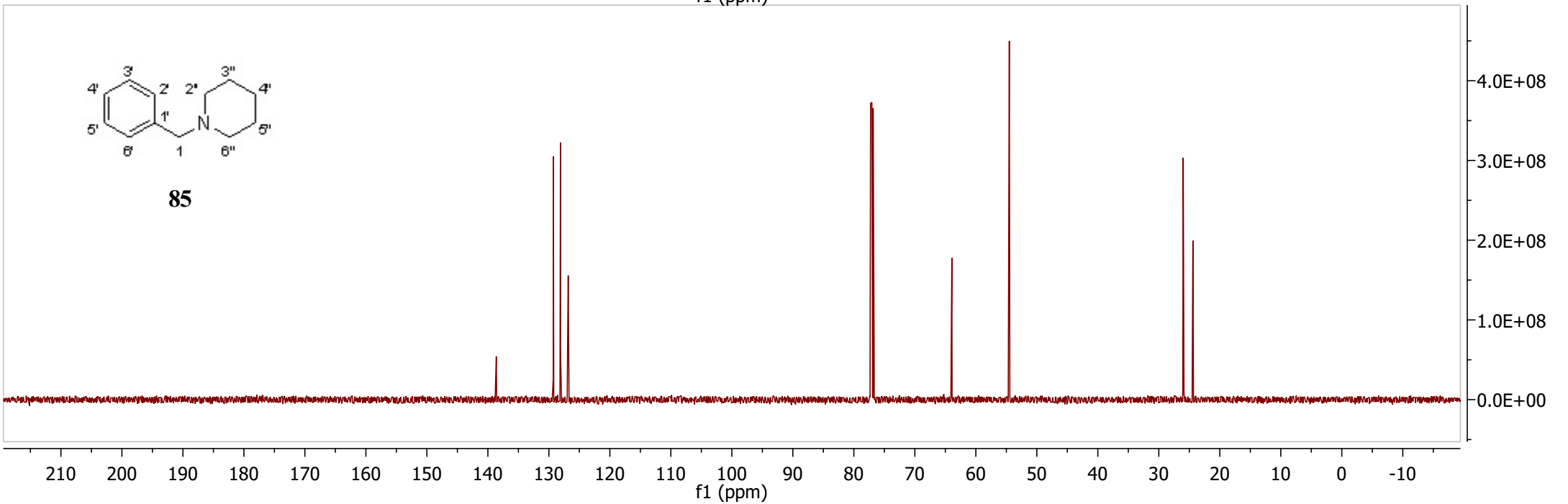


Plate 75b, CDCl3, 13C
138.62
129.27
128.10
126.83
63.93
54.51
26.00
24.41
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
-1.00E+08
140 138 136 134 132 130 128 126 124 122 120 68 66 64 62 60 58 56 54 28 26 24
f1 (ppm)


3'
4'
2'
2"
3"
4'
1'
N
5'
5"
6'
1
6"
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

85

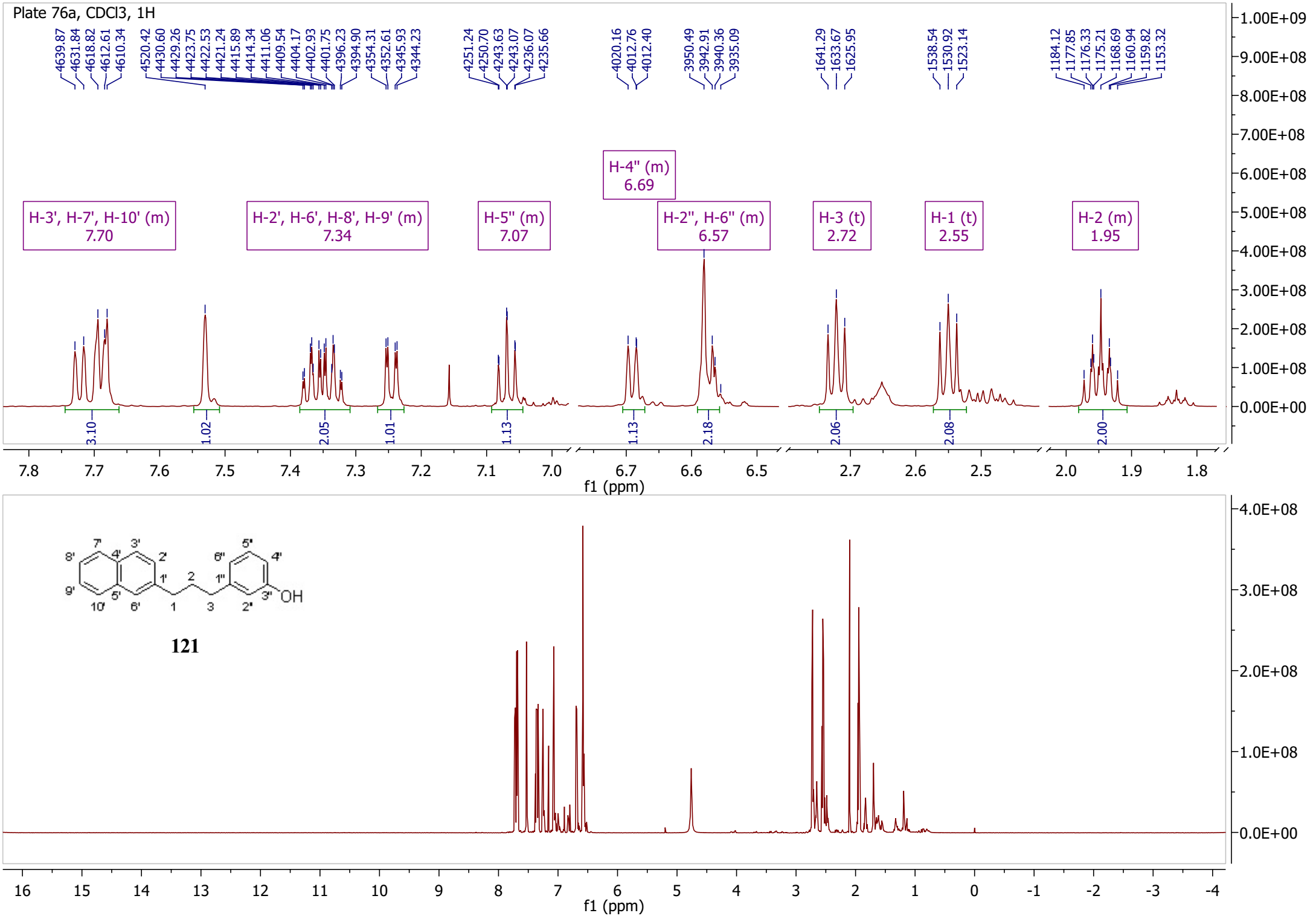


Plate 76a, CDCl3, 1H
4639.87
4631.84
4618.82
4612.61
4610.34
4520.42
4430.60
4429.26
4423.75
4422.53
4421.24
4415.89
4414.34
4411.06
4409.54
4404.17
4402.93
4401.75
4396.23
4394.90
4354.31
4352.61
4345.93
4344.23
4251.24
4250.70
4243.63
4243.07
4236.07
4235.66
4020.16
4012.76
4012.40
3950.49
3942.91
3940.36
3935.09
1641.29
1633.67
1625.95
1538.54
1530.92
1523.14
1184.12
1177.85
1176.33
1175.21
1168.69
1160.94
1159.82
1153.32
H-3', H-7', H-10' (m)
7.70
H-2', H-6', H-8', H-9' (m)
7.34
H-5" (m)
7.07
H-4" (m)
6.69
H-2", H-6" (m)
6.57
H-3 (t)
2.72
H-1 (t)
2.55
H-2 (m)
1.95
3.10
1.02
2.05
1.01
1.13
1.13
2.18
2.06
2.08
2.00
1.00E+09
9.00E+08
8.00E+08
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.7
6.6
6.5
2.7
2.6
2.5
2.0
1.9
1.8
f1 (ppm)
OH
121
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

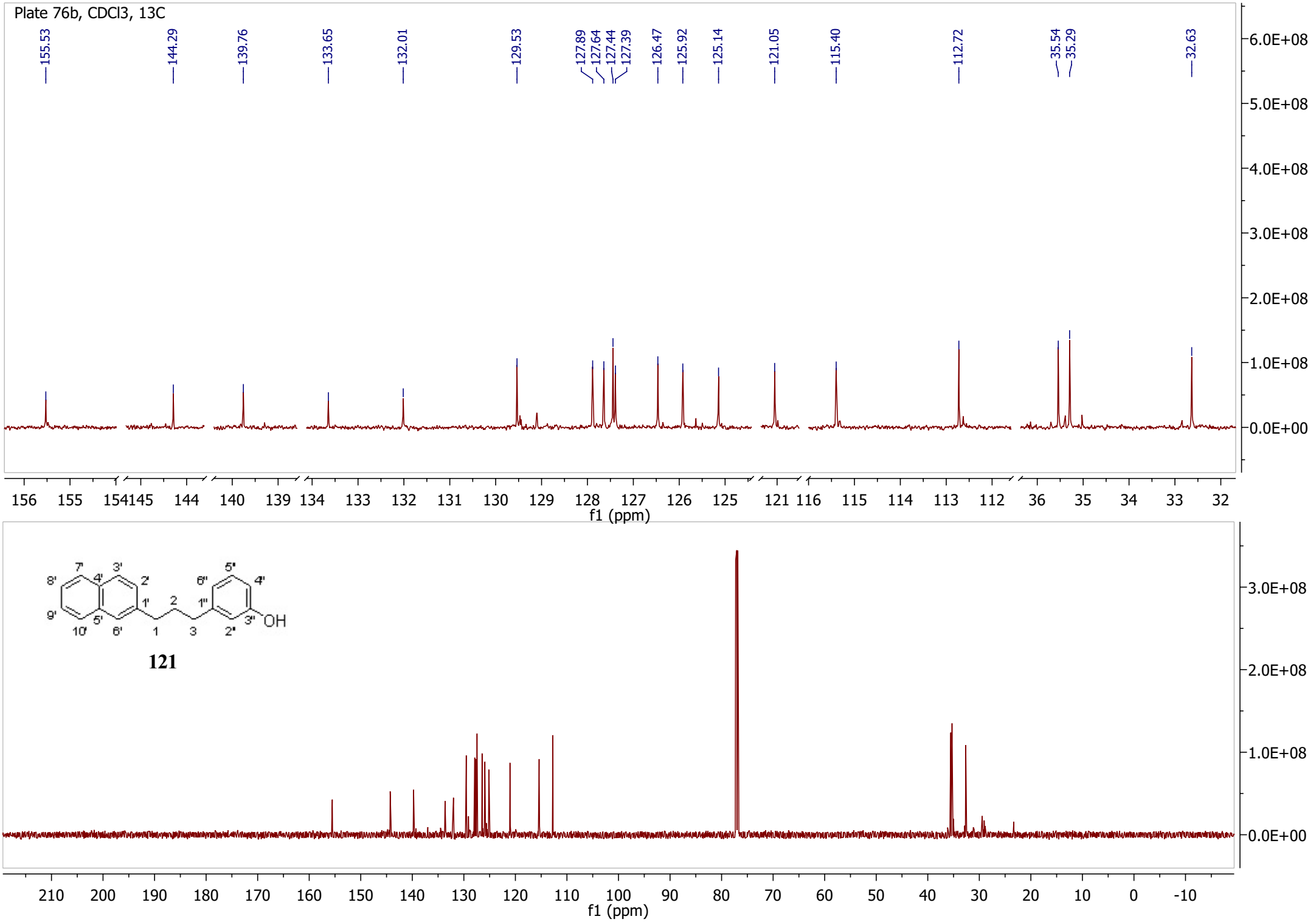


Plate 76b, CDCl3, 13C
155.53
144.29
139.76
133.65
132.01
129.53
127.89
127.64
127.44
127.39
126.47
125.92
125.14
121.05
115.40
112.72
35.54
35.29
32.63
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
156 155 154 145 144 140 139 134 133 132 131 130 129 128 127 126 125 121 116 115 114 113 112 36 35 34 33 32
f1 (ppm)
OH
121
3.0E+08
2.0E+08
1.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

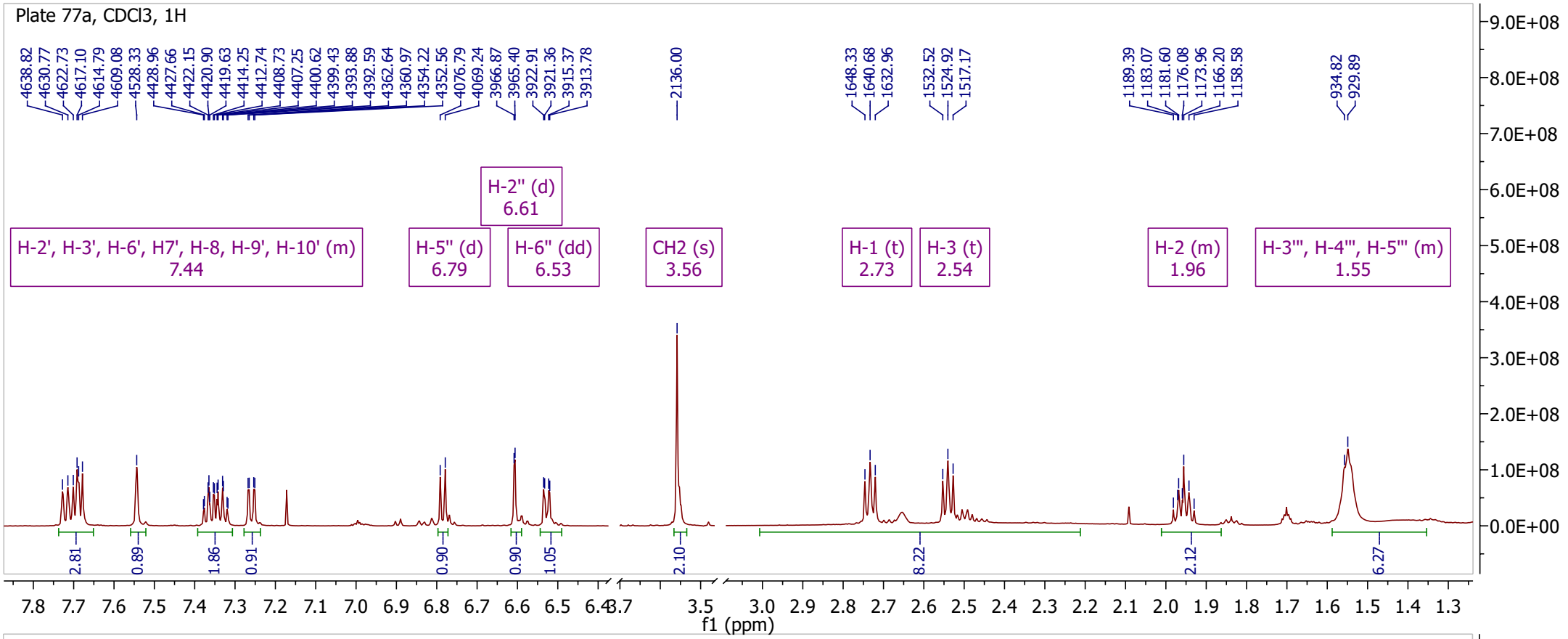
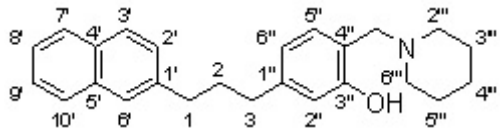


Plate 77a, CDCl3, 1H
4638.82
4630.77
4622.73
4617.10
4614.79
4609.08
4528.33
4428.96
4427.66
4422.15
4420.90
4419.63
4414.25
4412.74
4408.73
4407.25
4400.62
4399.43
4393.88
4392.59
4362.64
4360.97
4354.22
4352.56
4076.79
4069.24
3966.87
3965.40
3922.91
3921.36
3915.37
3913.78
2136.00
1648.33
1640.68
1632.96
1532.52
1524.92
1517.17
1189.39
1183.07
1181.60
1176.08
1173.96
1166.20
1158.58
934.82
929.89
H-2" (d)
6.61
H-2', H-3', H-6', H7', H-8, H-9', H-10' (m)
7.44
H-5" (d)
6.79
H-6" (dd)
6.53
CH2 (s)
3.56
H-1 (t)
2.73
H-3 (t)
2.54
H-2 (m)
1.96
H-3''', H-4''', H-5''' (m)
1.55
2.81
0.89
1.86
0.91
0.90
0.90
1.05
2.10
8.22
2.12
6.27
f1 (ppm)


7'
3'
8'
4'
2'
6"
5'
4"
2"'
3"'
N
1'
2
1"
6"'
9'
5'
3"
OH
4"'
10'
6'
1
3
2"
5"'

95

f1 (ppm)

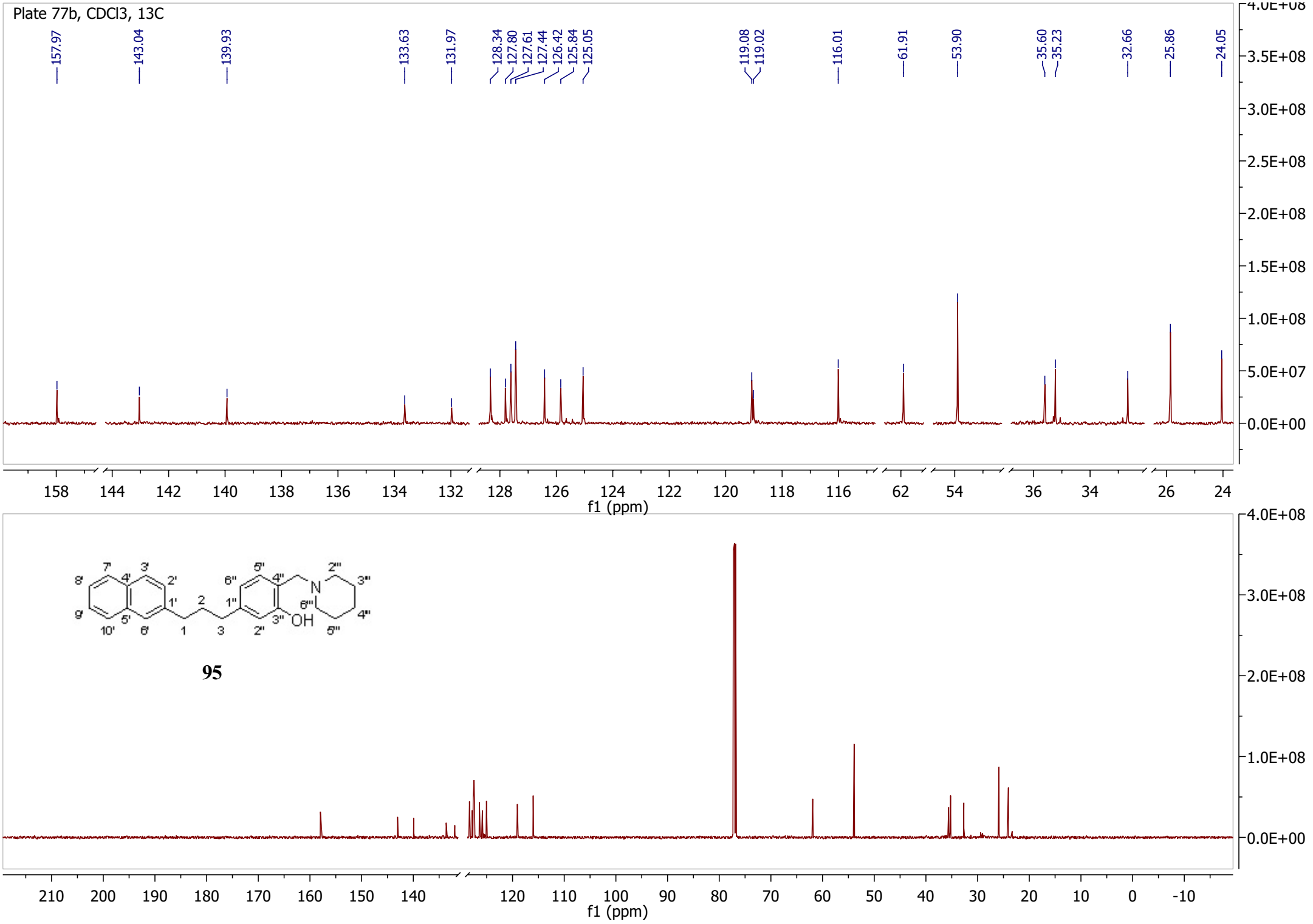


Plate 77b, CDCl3, 13C
157.97
143.04
139.93
133.63
131.97
128.34
127.80
127.61
127.44
126.42
125.84
125.05
119.08
119.02
116.01
61.91
53.90
35.60
35.23
32.66
25.86
24.05
f1 (ppm)
95

Appendix B

1.1 Antimalarial bioactivity screening

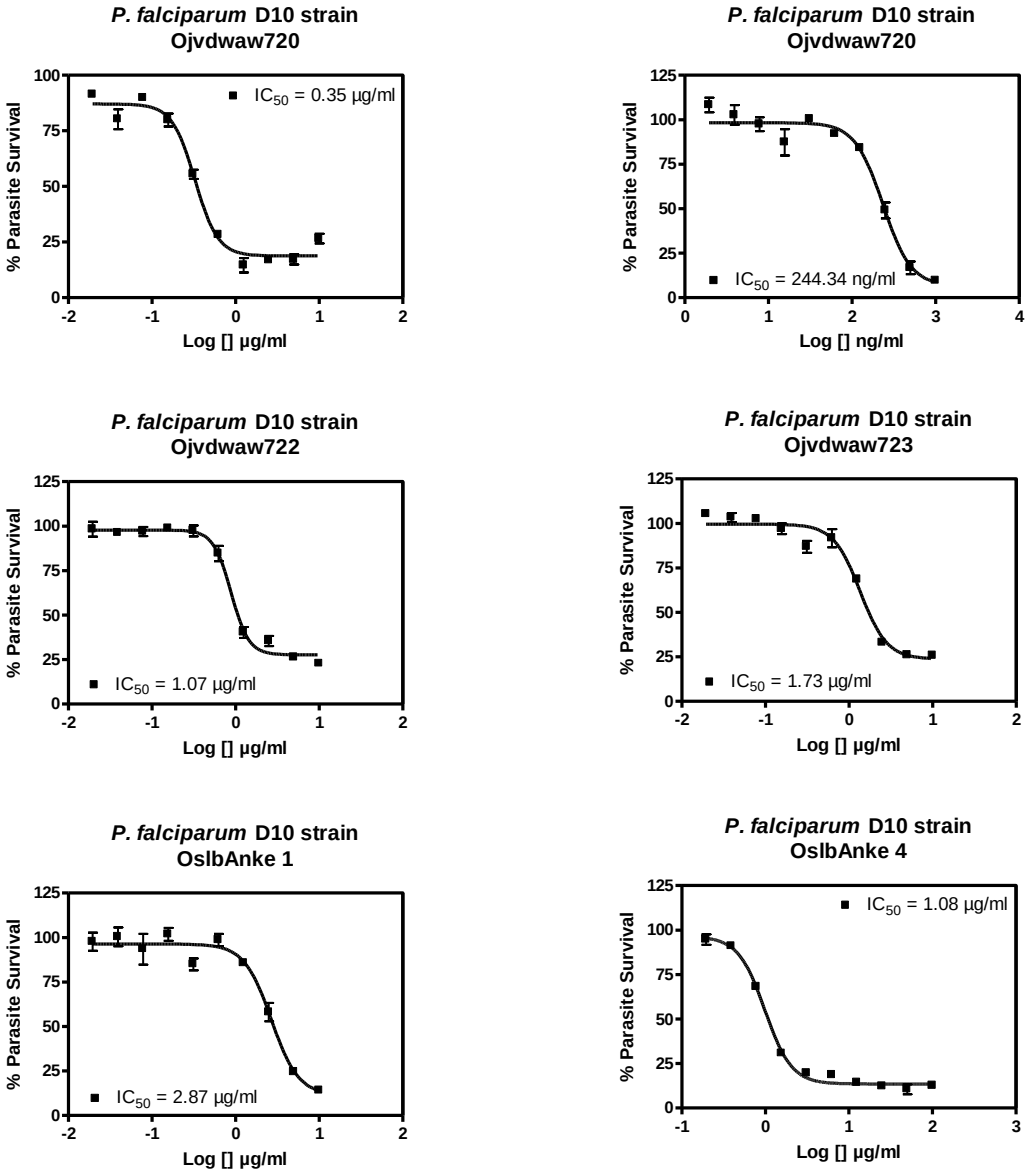


Figure 1: Dose-response curves of test samples against the CQS D10 strain of *P. falciparum* for compound **39**, **41**, **43**, **44** and **45**.

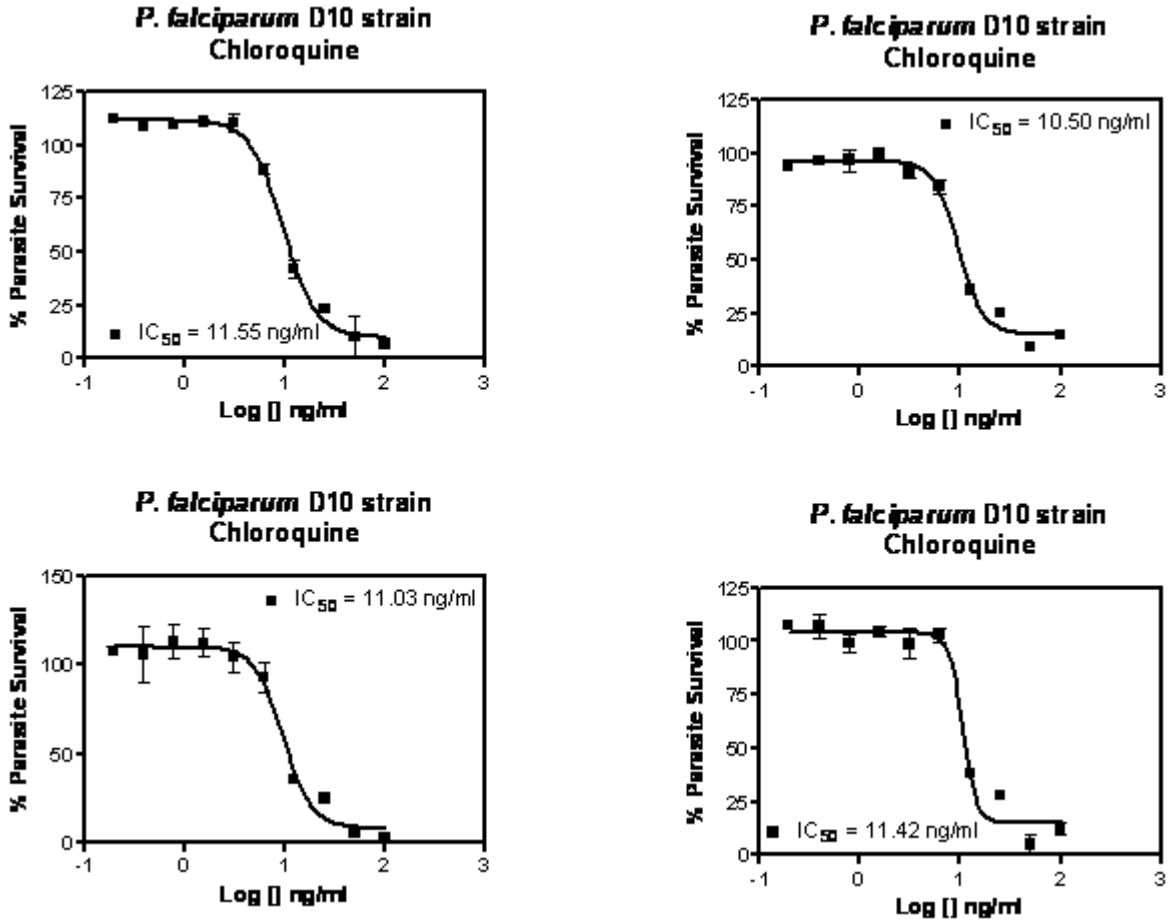


Figure 2: Dose-response curves of chloroquine against the CQS D10 strain of *P. falciparum.*

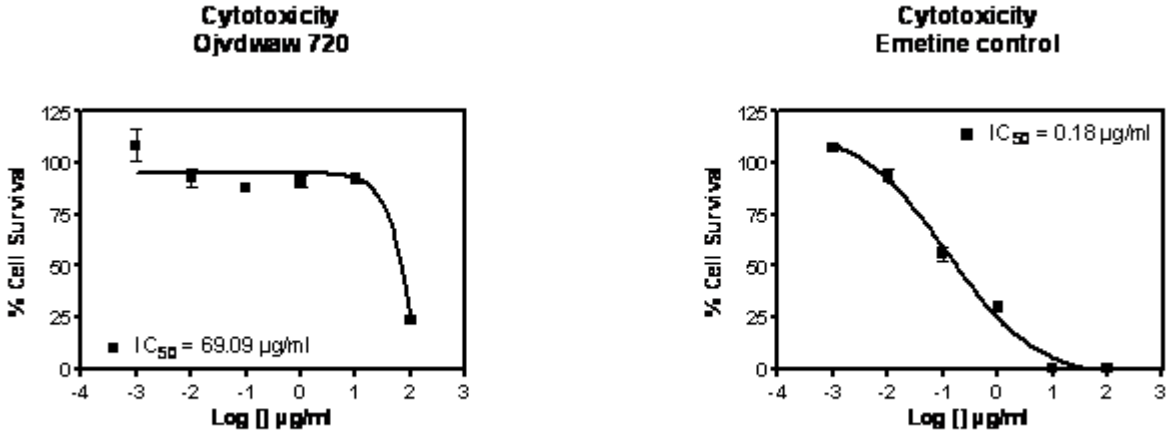


Figure 3: Dose-response curve of compound **41** against the CHO cell-line with emetine as control.

1.2 Anticancer bioactivity screening

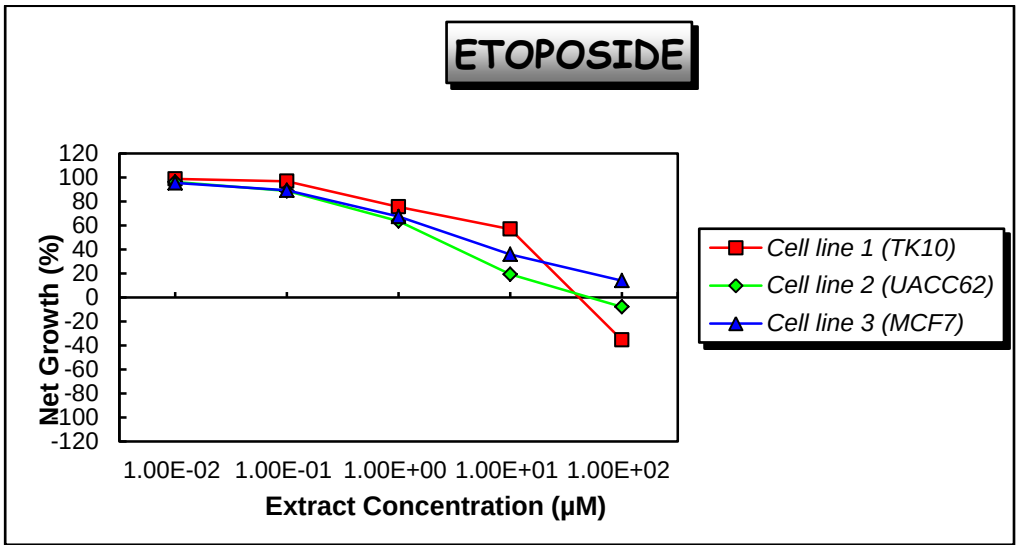
For each tested compound, four response parameters, GI50 (50% growth inhibition and signifies the growth inhibitory power of the test agent), TGI (which is the drug concentration resulting in total growth inhibition and signifies the cytostatic effect of the test agent), LC50 (50% lethal concentration and signifies the cytotoxic effect of the test agent), LC100 (100% lethal concentration and signifies the cytotoxic effect of the test agent), were calculated for each cell line.

Assay conditions

Compounds screened:	13
Test compound concentration:	100 - 0.01µM (5 x 10-fold serial dilutions)
Standard (Etoposide) concentration:	100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out:	Abs_{540}
Z' Factor :	0.9

Results

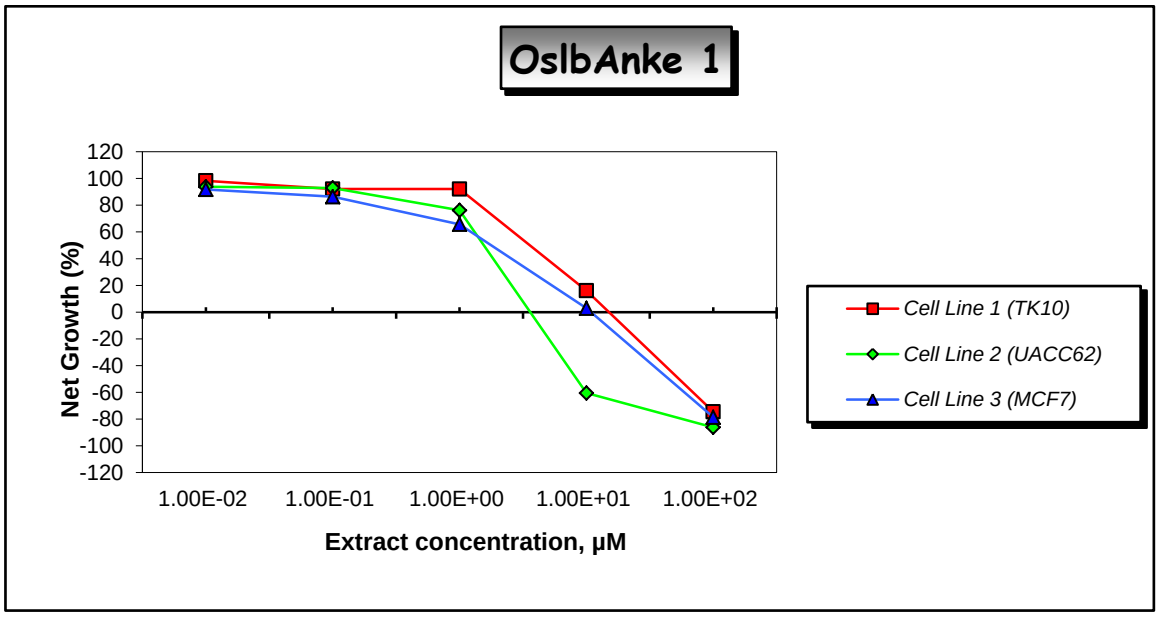
Etoposide



Activities	TK10	UACC62	MCF7
GI50	16.80	3.77	5.98
TGI	65.48	74.06	>100
LC50	>100	>100	>100
LC100	>100	>100	>100

Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-35.45	0.01	-7.81	0.03	14.03	0.02
10.00	56.99	0.00	19.30	0.01	35.89	0.03
1.00	75.53	0.00	63.62	0.03	67.45	0.02
0.10	96.81	0.01	88.80	0.04	89.30	0.03
0.01	98.76	0.01	96.23	0.04	95.43	0.44
Z factor	0.94		0.77		0.80	

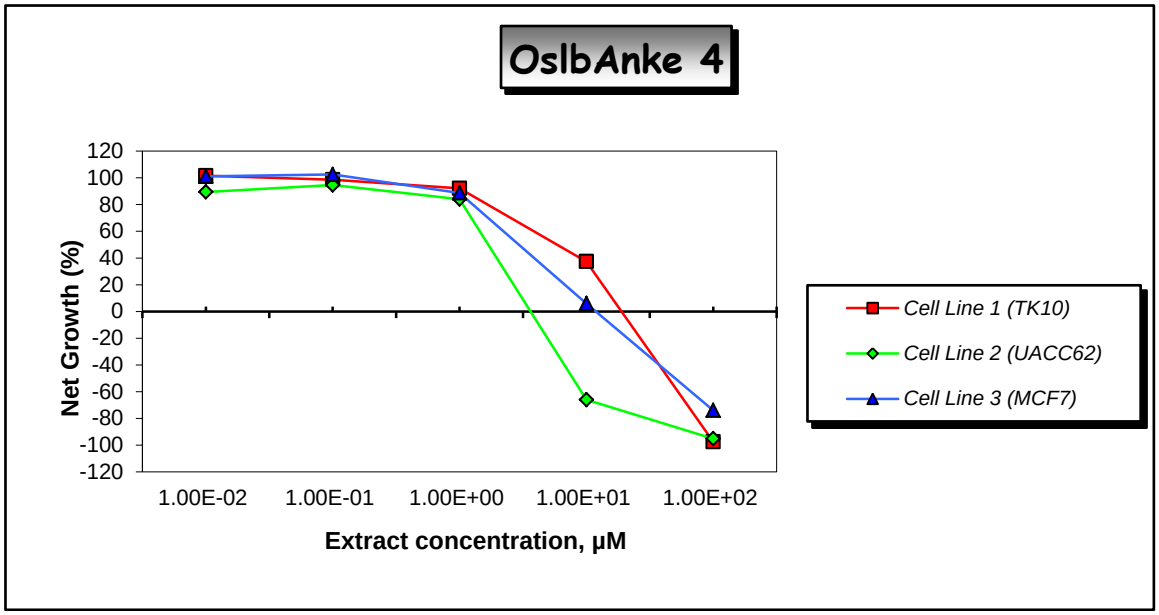
Compound 39



Activities	TK10	UACC62	MCF7
GI50	5.98	2.72	3.25
TGI	25.98	6.02	13.21
LC50	75.64	9.31	68.44
LC100	>100	>100	>100

Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-74.53	0.044	-86.17	0.001	-78.57	0.004
10.00	16.09	0.001	-60.51	0.007	2.90	0.006
1.00	92.08	0.008	76.19	0.024	65.69	0.023
0.10	92.08	0.039	92.86	0.020	86.37	0.038
0.01	98.28	0.002	93.80	0.023	91.78	0.021
Z factor	0.91		0.93		0.95	

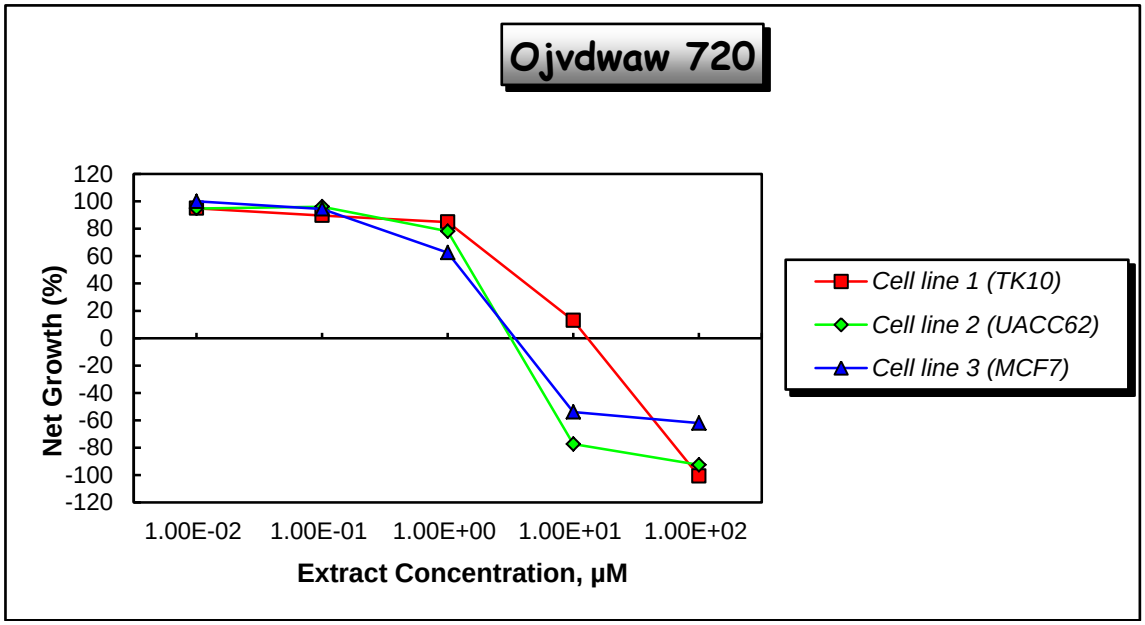
Compound 45



Activities	TK10	UACC62	MCF7
GI50	7.92	3.04	5.21
TGI	34.92	6.04	16.74
LC50	68.28	9.04	73.01
LC100	>100	>100	>100

Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-97.53	0.008	-95.17	0.002	-73.98	0.003
10.00	37.35	0.130	-66.01	0.007	5.98	0.000
1.00	92.09	0.040	84.03	0.016	88.67	0.017
0.10	98.55	0.019	94.61	0.033	102.49	0.001
0.01	101.58	0.003	89.40	0.005	101.10	0.023
Z factor	0.93		0.96		0.92	

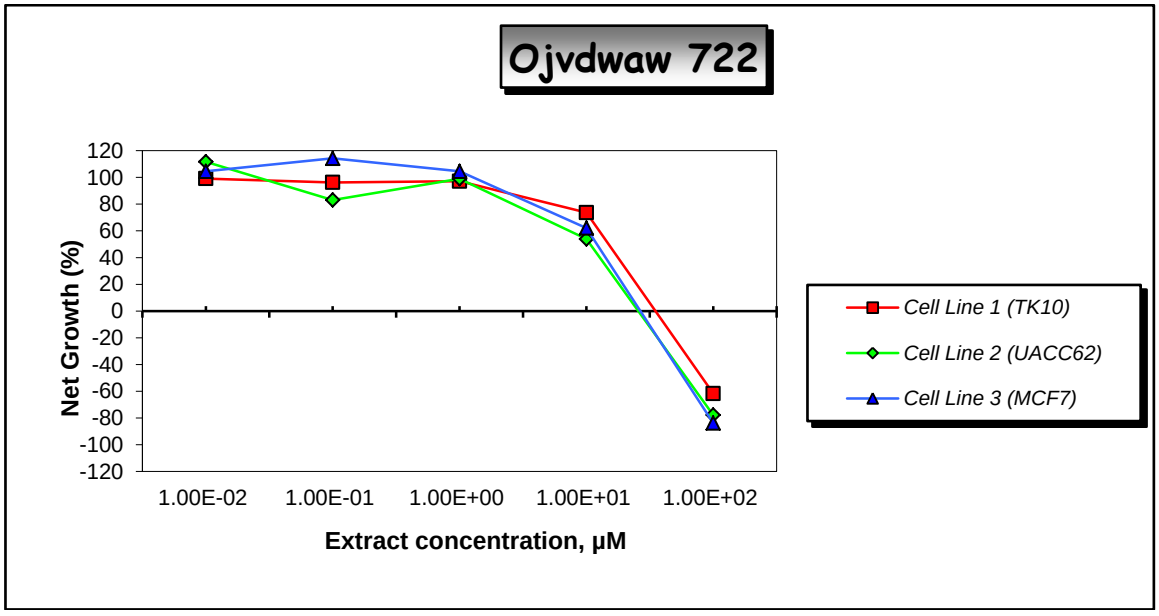
Compound 41



Activities	TK10	UACC62	MCF7
GI50	5.36	2.63	1.97
TGI	20.26	5.52	5.83
LC50	59.85	8.42	9.70
LC100	99.44	>100	>100

Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-100.71	0.002	-92.52	0.003	-62.03	0.003
10.00	12.95	0.000	-77.32	0.005	-53.88	0.003
1.00	84.83	0.049	78.10	0.030	62.54	0.029
0.10	89.66	0.032	96.06	0.013	94.41	0.017
0.01	94.87	0.053	94.77	0.008	99.97	0.269
Z factor	0.93		0.96		0.92	

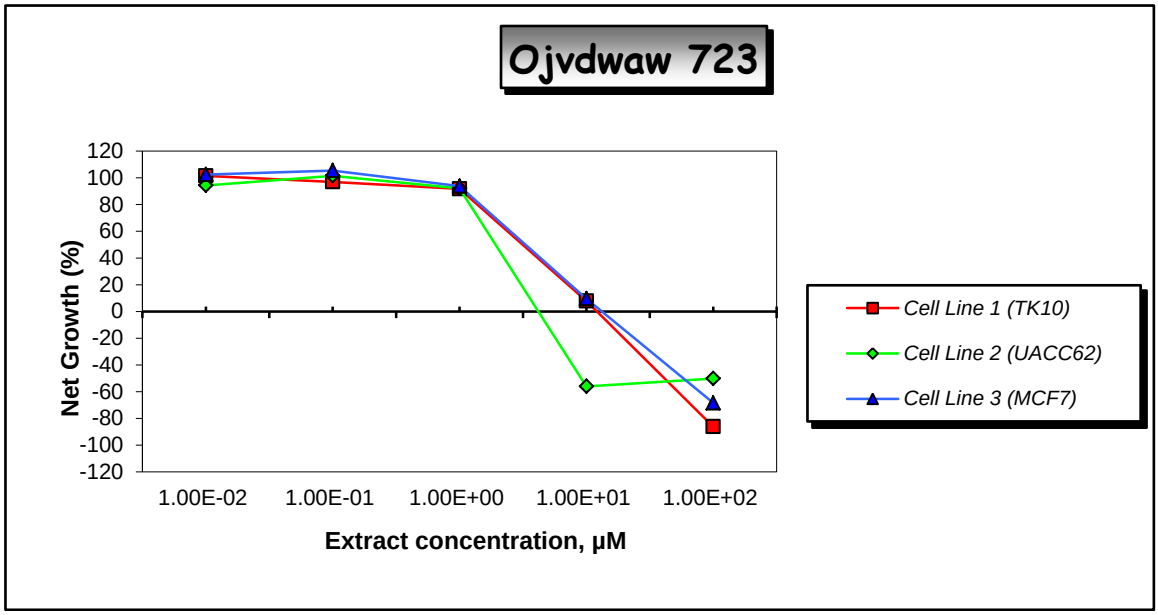
Compound 43



Activities	TK10	UACC62	MCF7
GI50	25.73	12.67	17.47
TGI	58.96	46.83	48.31
LC50	92.20	80.98	79.14
LC100	>100	>100	>100

Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-61.73	0.029	-77.84	0.000	-83.82	0.002
10.00	73.65	0.052	53.91	0.029	62.12	0.016
1.00	97.15	0.046	99.01	0.014	104.55	0.022
0.10	96.22	0.042	83.05	0.002	114.26	0.022
0.01	99.12	0.022	111.70	0.029	104.55	0.064
Z factor	0.96		0.92		0.88	

Compound 44



Activities	TK10	UACC62	MCF7
GI50	5.48	3.56	5.68
TGI	17.48	6.60	21.06
LC50	65.34	9.63	78.74
LC100	>100	>100	>100

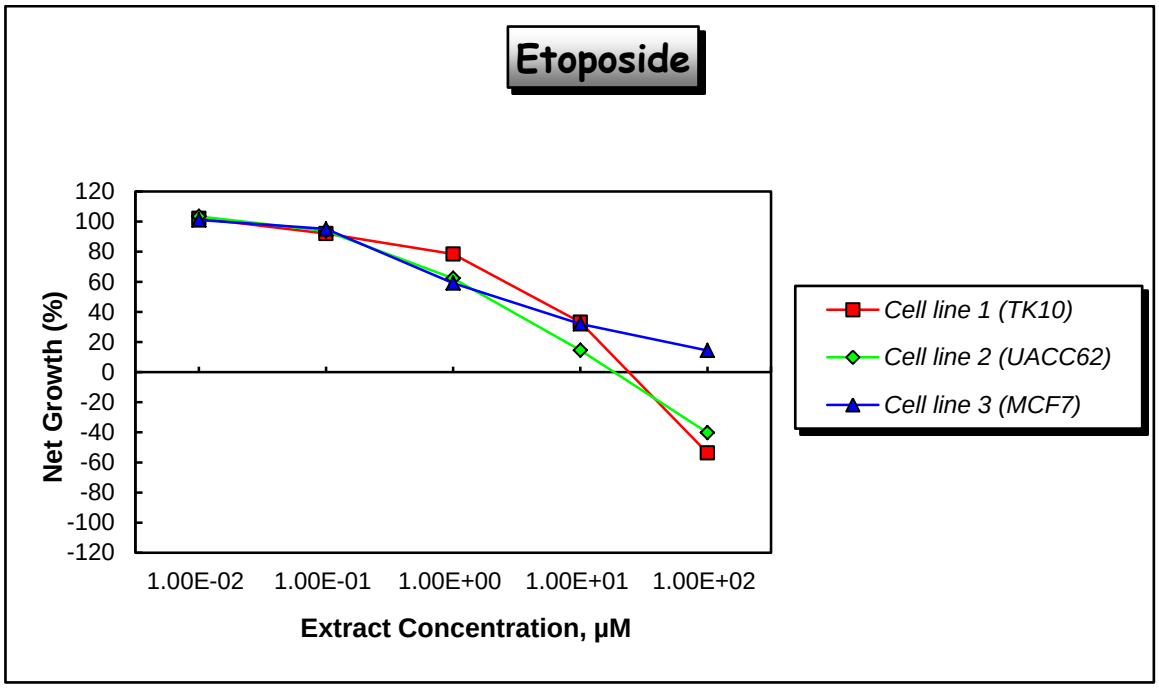
Concentration, µM	%GI TK10	STD	%GI UACC62	STD	%GI MCF7	STD
100.00	-86.21	0.014	-50.14	0.002	-68.43	0.005
10.00	7.81	0.013	-56.01	0.003	9.58	0.012
1.00	91.74	0.014	92.08	0.035	93.75	0.027
0.10	96.93	0.009	101.48	0.024	105.44	0.031
0.01	101.43	0.006	94.32	0.022	102.44	0.002
Z factor	0.86		0.91		0.93	

Assay conditions

Compounds screened:	7
Test compound concentration:	100 - 0.01µM (5 x 10-fold serial dilutions)
Standard (Etoposide) concentration:	100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out:	Abs_{540}
Z' Factor :	0.9

Results

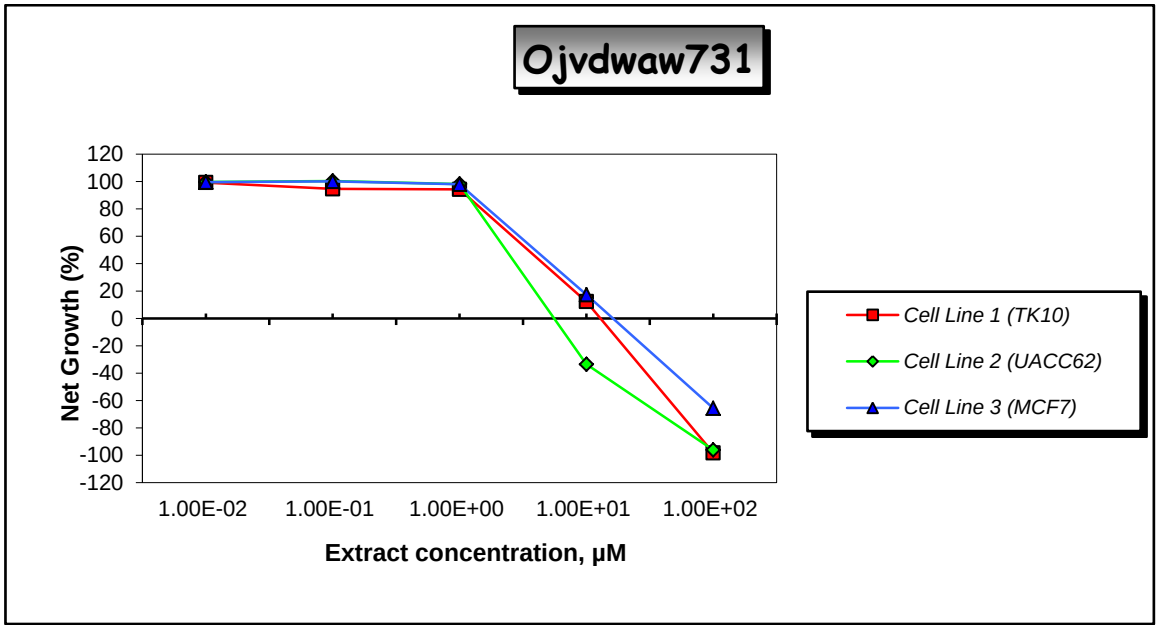
Etoposide



Activities	TK10	UACC62	MCF7
GI50	**6.65**	**3.32**	**4.03**
TGI	**44.35**	**33.87**	**>100**
LC50	**96.14**	**>100**	**>100**
LC100	**>100**	**>100**	**>100**

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth,% MCF7	STD
100	-53.73	0.002	-40.24	0.012	14.40	0.077
10	33.16	0.087	14.53	0.016	32.01	0.037
1	78.42	0.009	62.32	0.039	59.12	0.059
0.1	92.02	0.020	93.79	0.047	95.13	0.036
0.01	102.12	0.020	103.44	0.024	101.07	1.651
Z factor	0.91		0.88		0.98	

Compound 48



Activities	TK10	UACC62	MCF7
GI50	5.86	4.29	6.35
TGI	19.99	7.71	28.79
LC50	60.71	33.75	83.02
LC100	>100	>100	>100

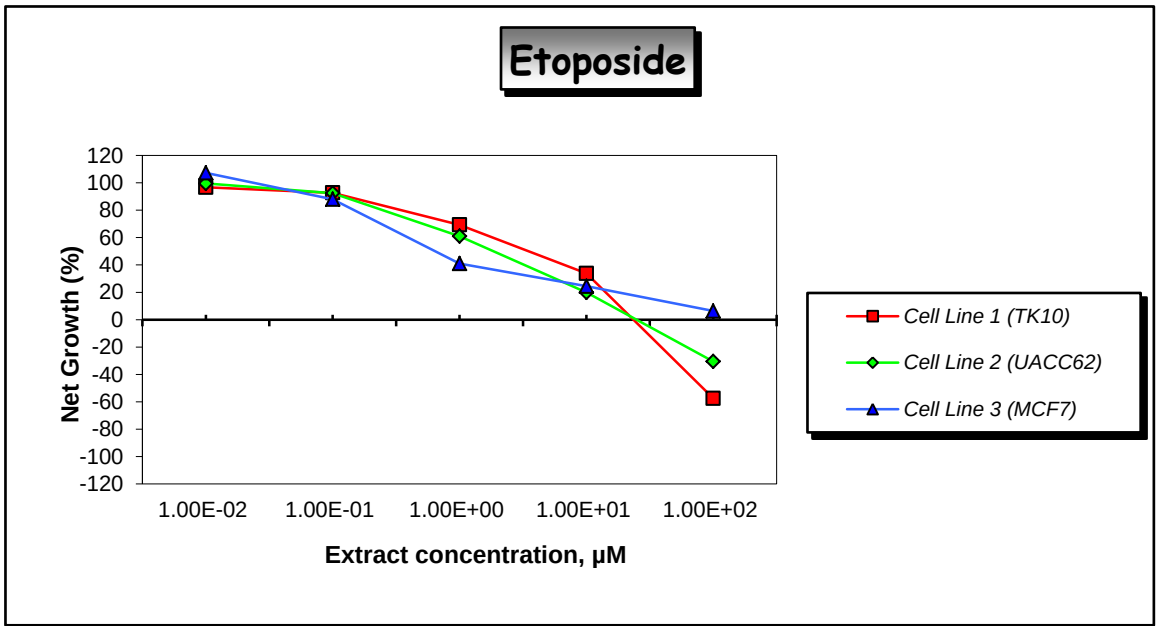
Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growt,% MCF7	STD
100	-98.25	0.004	-96.08	0.012	-65.66	0.010
10	12.27	0.018	-33.48	0.000	17.33	0.042
1	94.26	0.008	98.21	0.056	97.99	0.009
0.1	94.63	0.028	100.39	0.009	100.13	0.011
0.01	99.24	0.017	99.69	0.046	99.50	0.020
Z factor	0.91		0.88		0.98	

Assay conditions

Samples screened: 6
Test sample concentration: 100 - 0.01µM (5 x 2-fold serial dilutions)
Standard (Etoposide) concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out: Abs_{540}
Z' Factor : 0.8- 0.9

Results

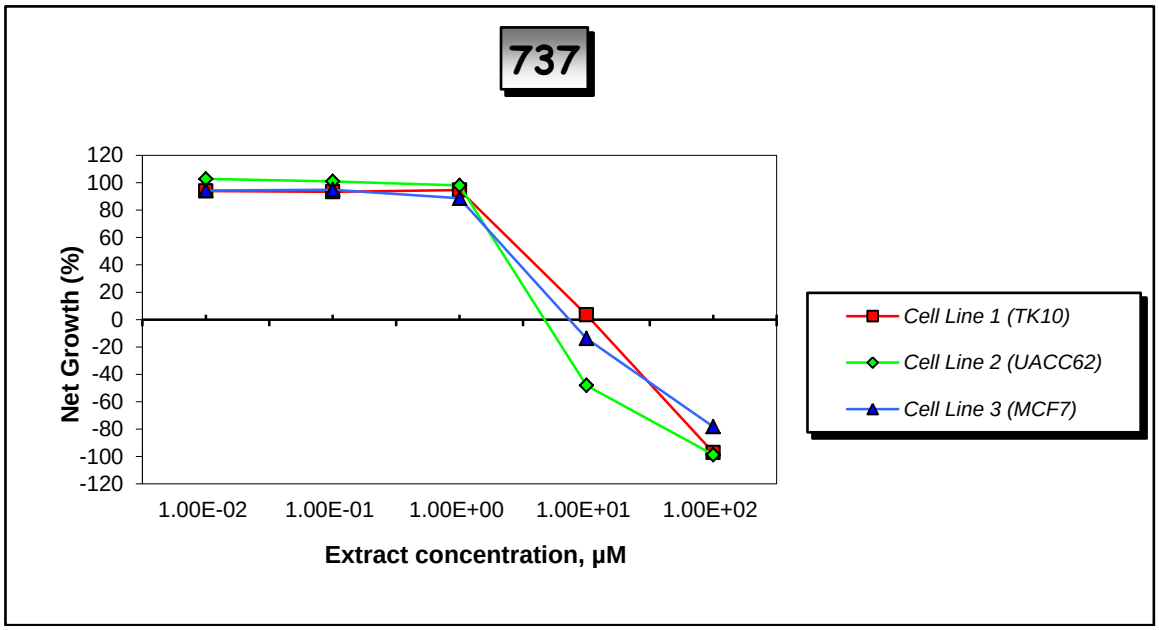
Etoposide



Activities	TK10	UACC62	MCF7
GI50	5.89	3.41	0.83
TGI	43.33	45.52	>100
LC50	92.61	>100	>100
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-57.49	0.013	-30.54	0.007	6.38	0.046
10	33.81	0.014	19.91	0.012	24.46	0.036
1	69.30	0.076	61.01	0.063	41.00	0.038
0.1	92.66	0.066	92.48	0.020	88.00	0.013
0.01	96.71	0.070	99.50	0.006	107.27	0.008
Z factor	0.78		0.92		0.62	

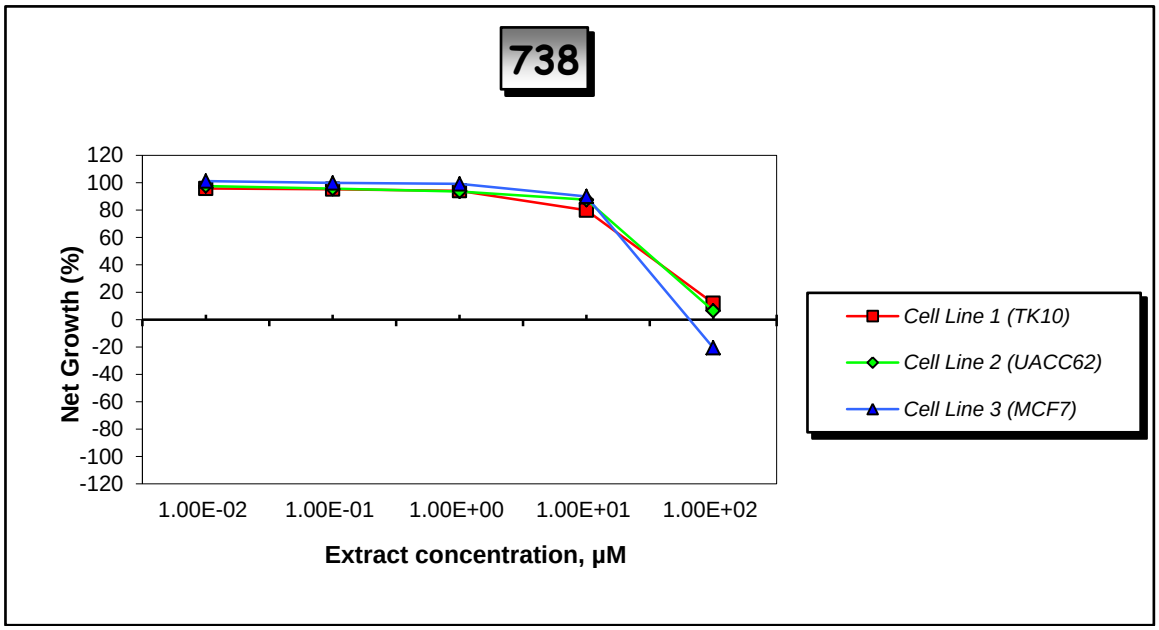
Compound 40



Activities	TK10	UACC62	MCF7
GI50	5.41	3.96	4.40
TGI	13.18	7.04	8.79
LC50	57.88	13.42	60.61
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-97.11	0.004	-98.72	0.001	-78.23	0.013
10	3.55	0.006	-48.08	0.025	-13.73	0.028
1	94.68	0.062	97.99	0.003	88.62	0.081
0.1	93.38	0.051	100.96	0.052	94.88	0.090
0.01	93.95	0.024	102.78	0.067	94.34	0.009
Z factor	0.90		0.84		0.75	

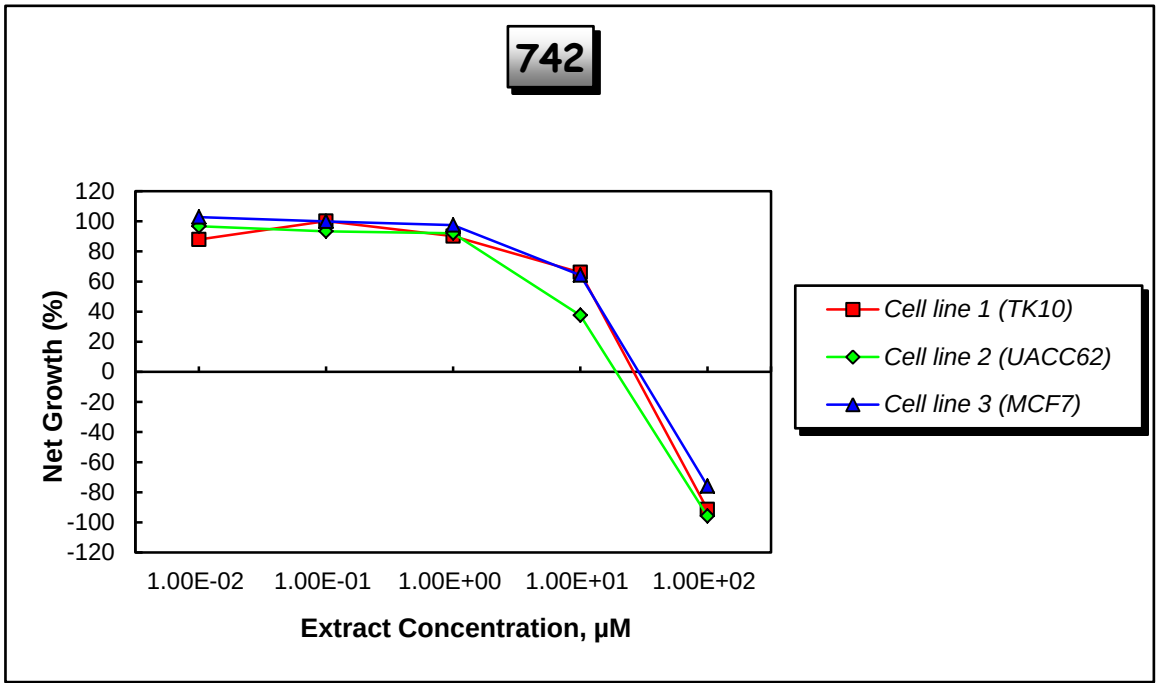
Compound 63



Activities	TK10	UACC62	MCF7
GI50	49.60	51.72	42.55
TGI	>100	>100	83.26
LC50	>100	>100	>100
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	11.95	0.038	6.46	0.001	-20.56	0.007
10	79.89	0.008	87.63	0.038	89.97	0.056
1	94.07	0.016	93.63	0.043	99.15	0.023
0.1	95.27	0.008	95.65	0.024	99.87	0.132
0.01	95.78	0.005	97.61	0.054	101.23	0.147
Z factor	0.85		0.85		0.80	

Compound 64



Activities	TK10	UACC62	MCF7
GI50	19.15	7.94	19.14
TGI	47.72	35.33	51.25
LC50	76.29	69.07	83.35
LC100	>100	>100	>100

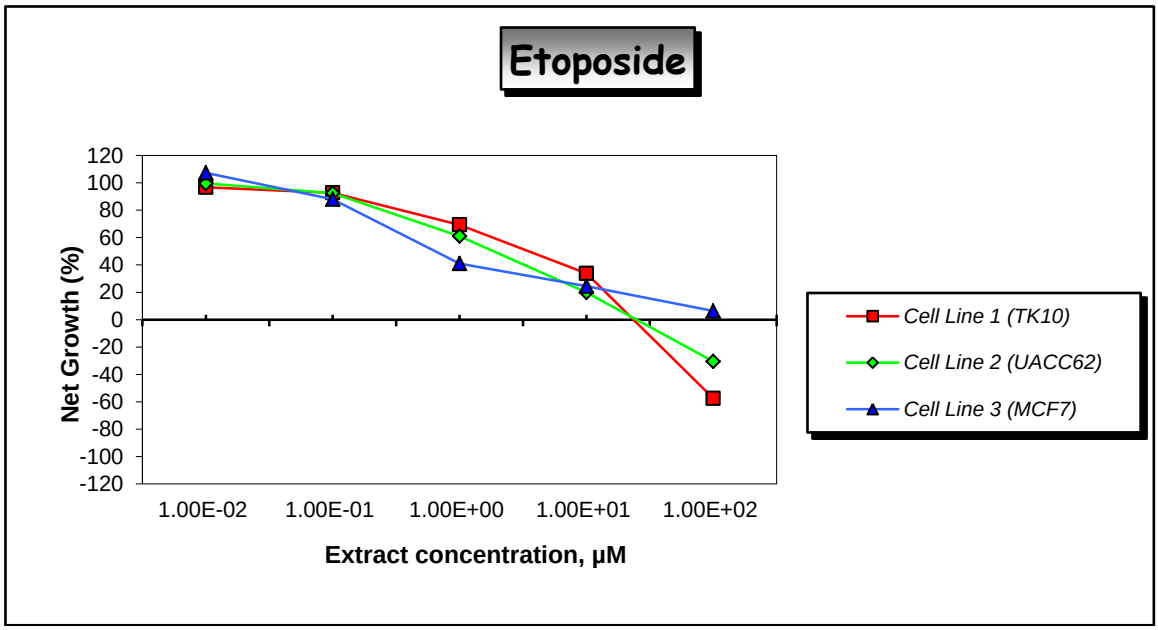
Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-91.49	0.000	-95.82	0.006	-75.93	0.012
10	66.01	0.052	37.53	0.066	64.24	0.051
1	90.10	0.033	92.05	0.006	97.47	0.036
0.1	100.09	0.089	93.36	0.003	99.93	0.091
0.01	87.89	0.009	96.70	0.051	102.80	1.097
Z factor	0.85		0.85		0.80	

Assay conditions

Samples screened: 5
Test sample concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)
Standard (Etoposide) concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out: Abs_{540}
Z' Factor : 0.8- 0.9

Results

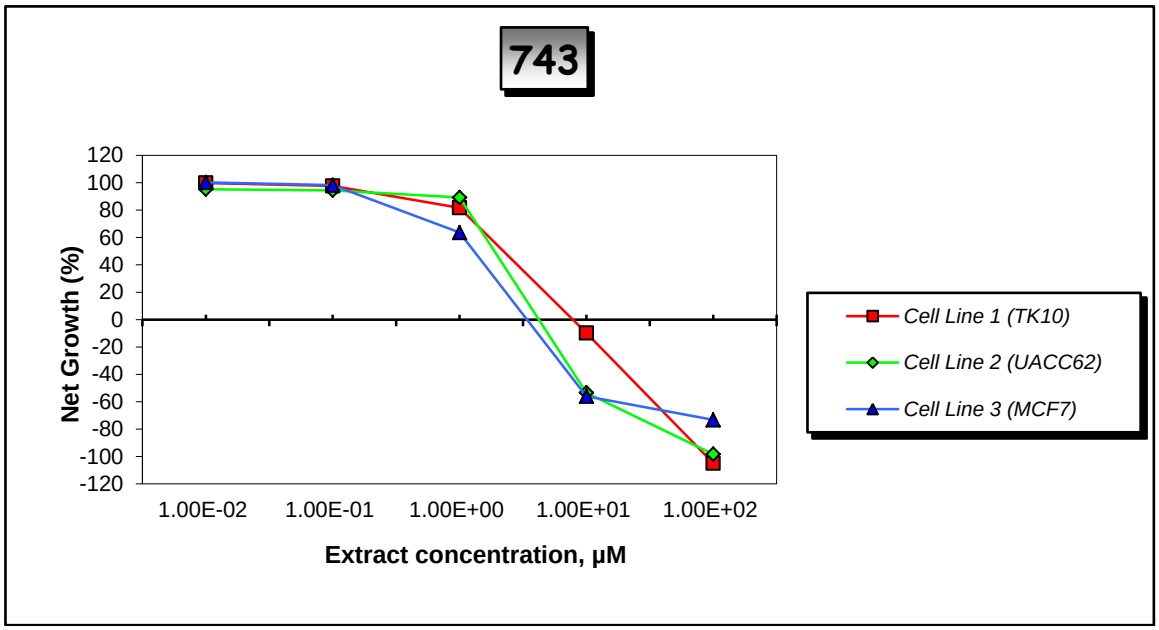
Etoposide



Activities	TK10	UACC62	MCF7
GI50	5.89	3.41	0.83
TGI	43.33	45.52	>100
LC50	92.61	>100	>100
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-57.49	0.013	-30.54	0.007	6.38	0.046
10	33.81	0.014	19.91	0.012	24.46	0.036
1	69.30	0.076	61.01	0.063	41.00	0.038
0.1	92.66	0.066	92.48	0.020	88.00	0.013
0.01	96.71	0.070	99.50	0.006	107.27	0.008
Z factor	0.78		0.92		0.62	

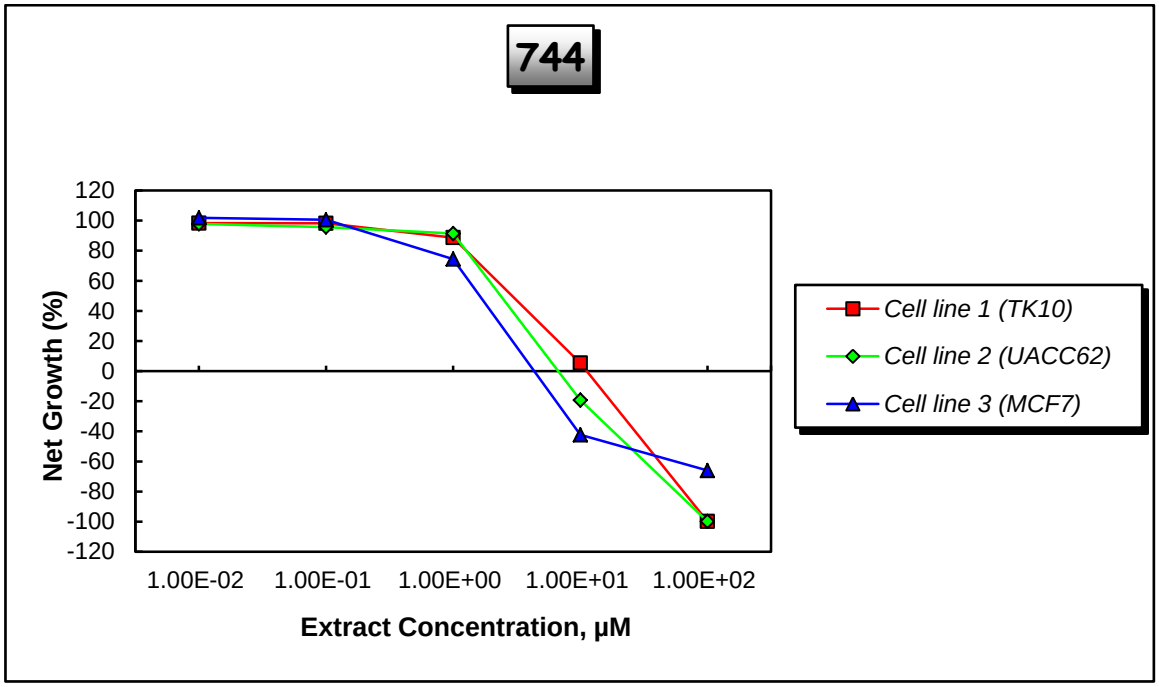
Compound 46



Activities	TK10	UACC62	MCF7
GI50	4.12	3.48	2.03
TGI	9.04	6.63	5.79
LC50	48.06	9.79	9.55
LC100	95.35	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth,% MCF7	STD
100	-104.91	0.001	-98.32	0.002	-73.24	0.007
10	-9.77	0.025	-53.41	0.028	-56.02	0.015
1	81.70	0.013	89.25	0.033	63.66	0.013
0.1	97.65	0.002	94.42	0.038	98.25	0.035
0.01	99.81	0.040	95.27	0.067	100.23	0.033
Z factor	0.88		0.96		0.91	

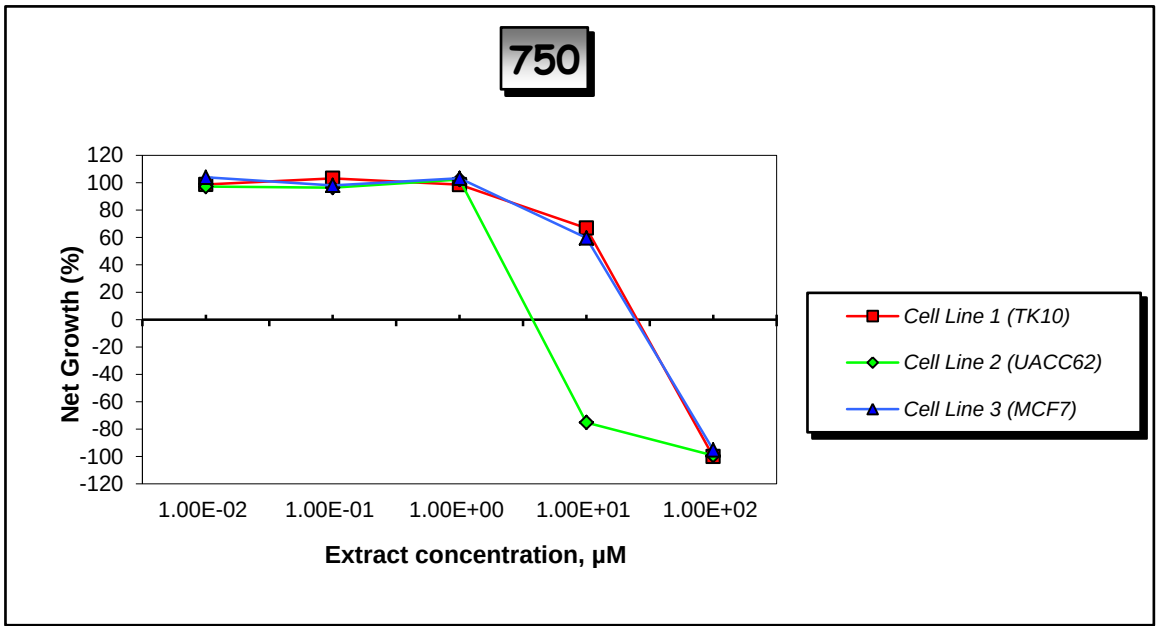
Compound 47



Activities	TK10	UACC62	MCF7
GI50	5.18	4.37	2.88
TGI	14.59	8.43	6.74
LC50	57.34	44.31	39.14
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth,% MCF7	STD
100	-99.90	0.003	-99.85	0.001	-66.01	0.011
10	5.36	0.001	-19.29	0.020	-42.33	0.056
1	88.66	0.082	91.38	0.079	74.44	0.017
0.1	98.17	0.004	95.70	0.044	100.51	0.007
0.01	98.27	0.044	97.79	0.005	101.81	1.017
Z factor	0.88		0.96		0.91	

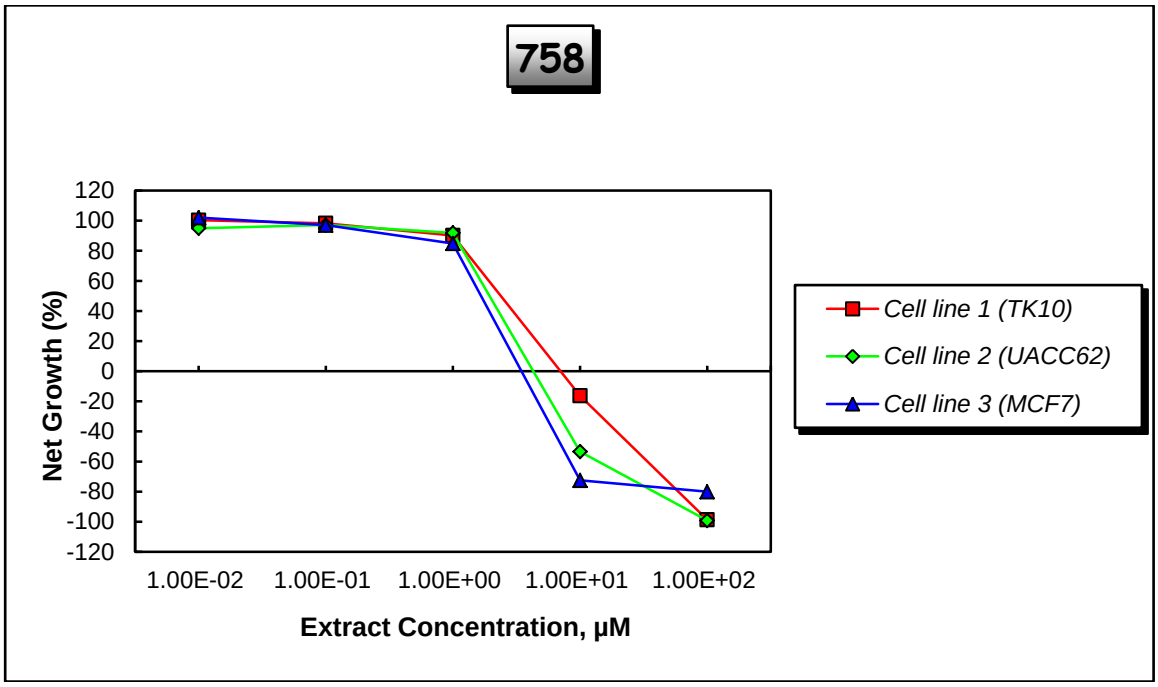
Compound 65



Activities	TK10	UACC62	MCF7
GI50	19.09	3.65	15.61
TGI	46.05	6.19	44.66
LC50	73.00	8.72	73.71
LC100	99.96	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth,% MCF7	STD
100	-100.07	0.000	-99.30	0.001	-95.24	0.012
10	66.86	0.046	-75.15	0.017	59.65	0.019
1	98.58	0.003	102.33	0.049	103.24	0.023
0.1	103.19	0.002	96.44	0.014	98.05	0.092
0.01	98.68	0.046	97.19	0.039	103.96	0.127
Z factor	0.88		0.85		0.83	

Compound 42



Activities	TK10	UACC62	MCF7
GI50	4.39	3.59	2.99
TGI	8.62	6.69	5.85
LC50	46.78	9.79	8.71
LC100	>100	>100	>100

Concentration, µM	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth,% MCF7	STD
100	-98.70	0.001	-99.20	0.000	-80.04	0.005
10	-16.34	0.043	-53.45	0.089	-72.51	0.005
1	90.14	0.068	91.85	0.000	84.84	0.040
0.1	98.24	0.055	97.13	0.009	97.03	0.009
0.01	100.29	0.045	94.94	0.029	101.99	1.055
Z factor	0.93		0.93		0.76	

1.3 Cytotoxicity screening

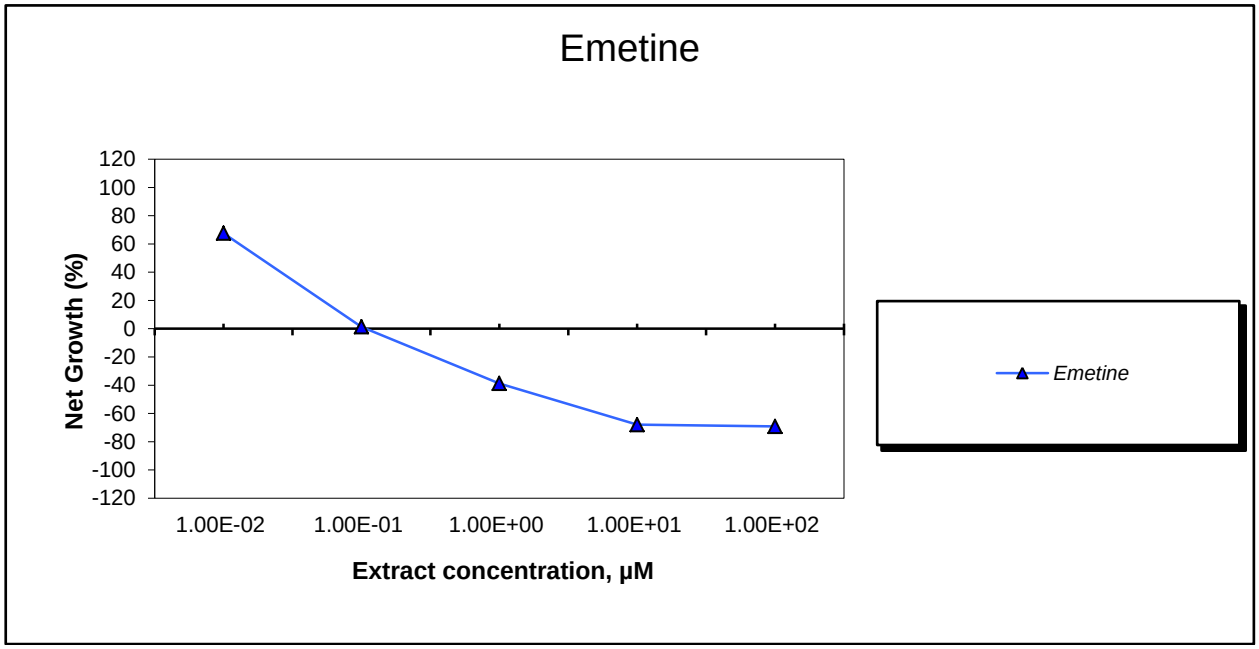
Assay conditions

Samples screened: 6
Test sample concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)

Standard (Emetine) concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out: Abs_{540}
Z' Factor : 0.9

Results

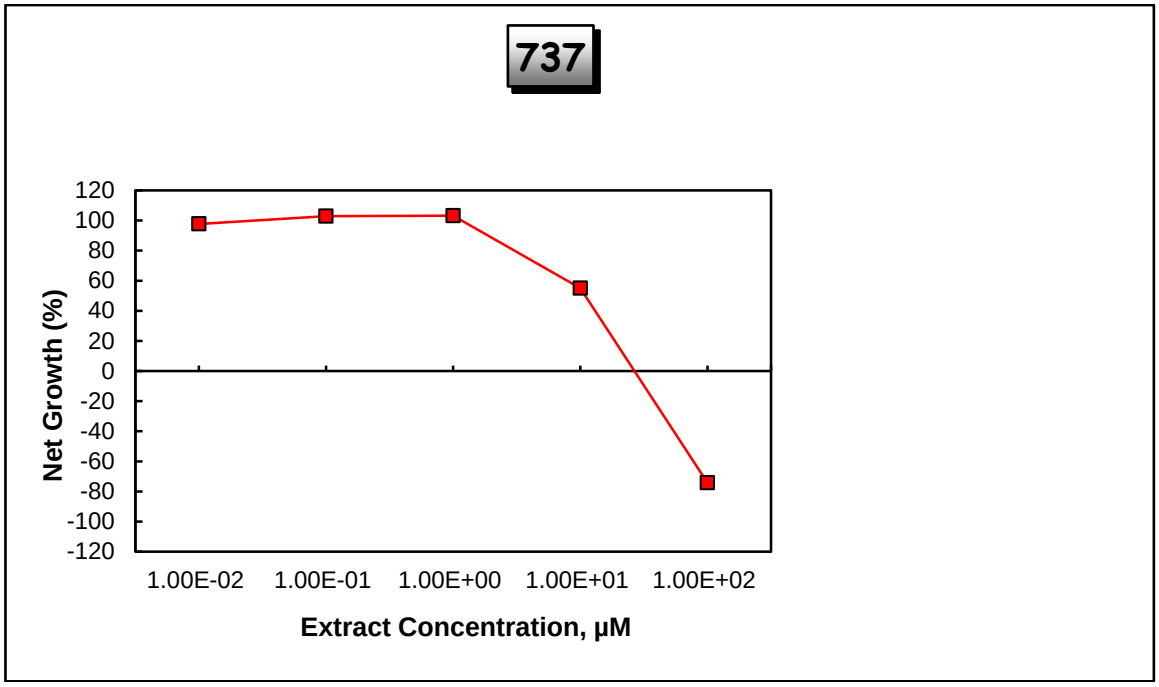
Emetine



Activities	
GI50	0.03
TGI	0.13
LC50	4.46
LC100	>100

Concentration, µM	Cell Growth, %	STD
100	-69.15	0.018
10	-67.95	0.036
1	-38.77	0.012
0.1	1.34	0.006
0.01	67.57	0.048
Z factor	0.92	

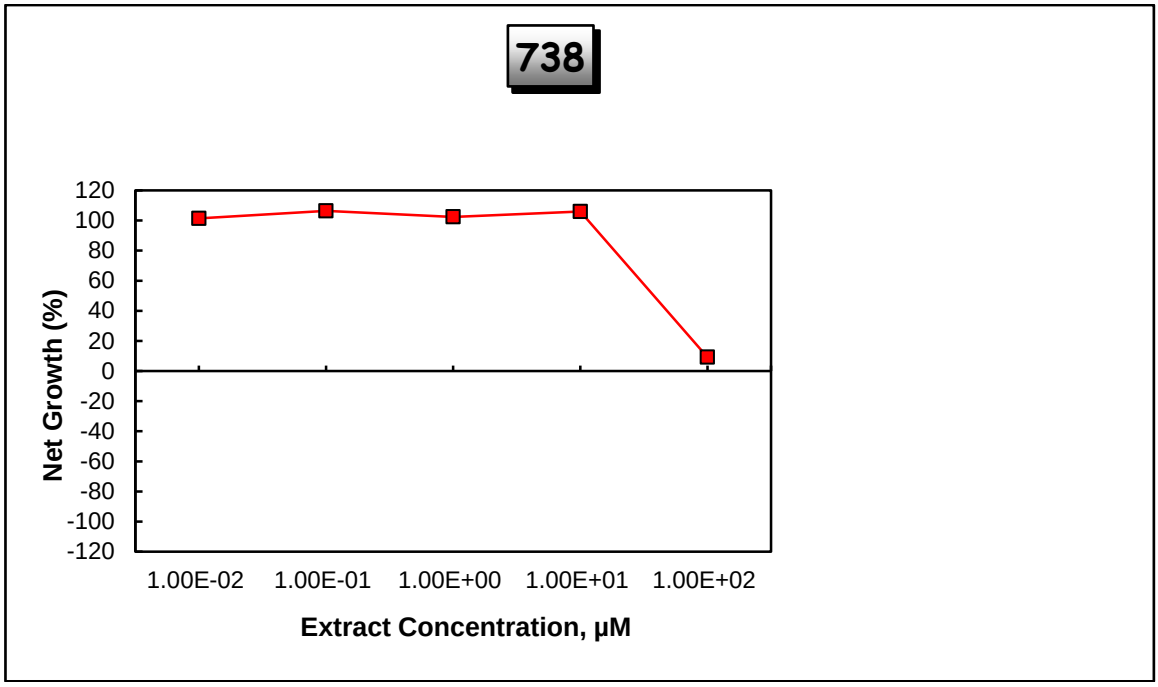
Compound 40



Activities	
GI50	13.50
TGI	48.30
LC50	83.11
LC100	>100

Concentration, µM	Cell Growth,%	STD
100	-74.27	0.052
10	55.03	0.072
1	103.18	0.024
0.1	102.84	0.000
0.01	97.70	0.022
Z factor	0.87	

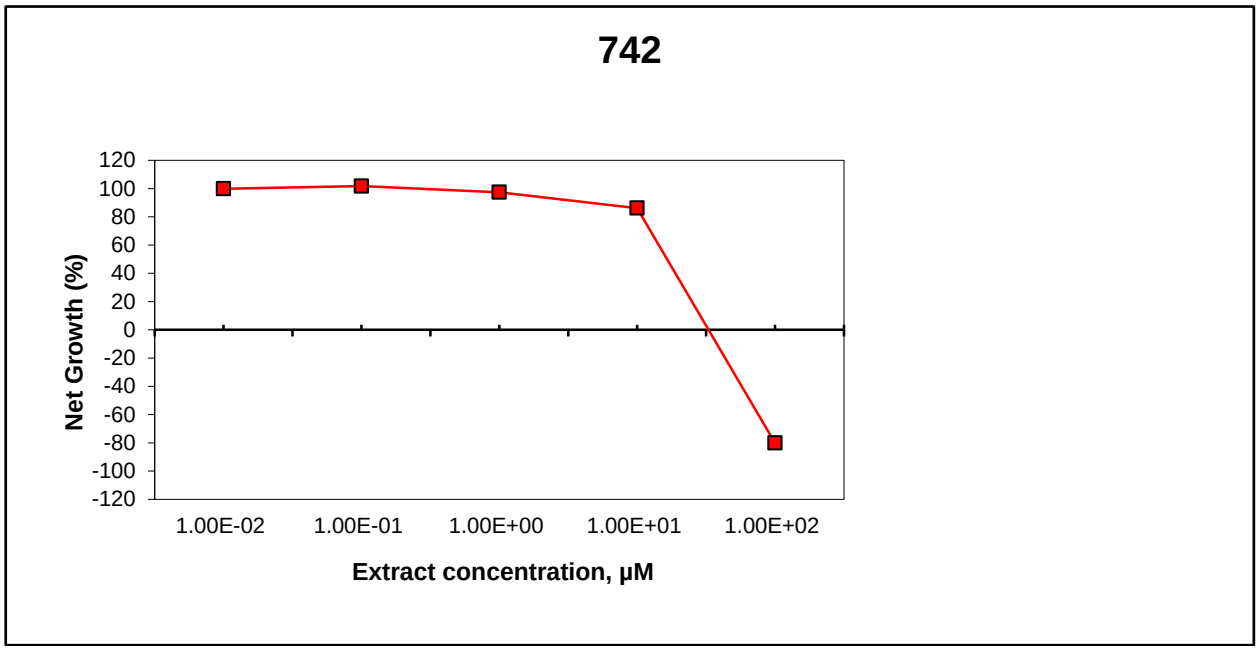
Compound 63



Activities	
GI50	62.02
TGI	>100
LC50	>100
LC100	>100

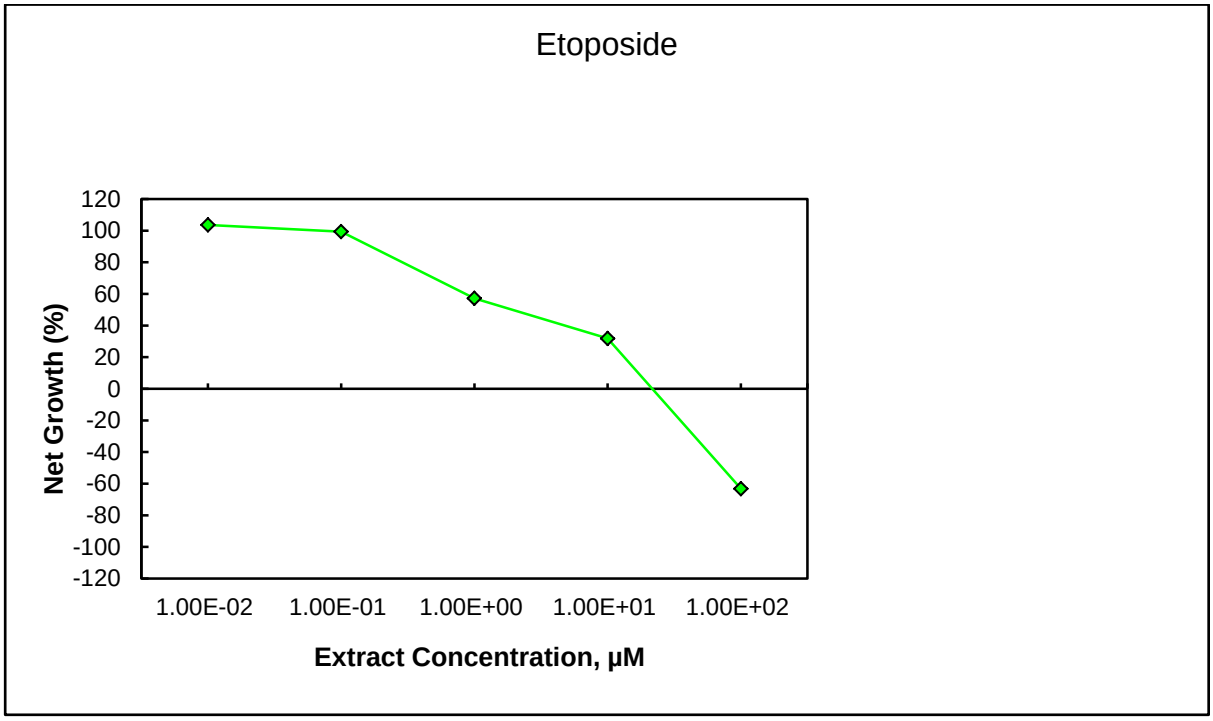
Concentration, µM	Cell Growth,%	STD
100	9.16	0.037
10	105.93	0.005
1	102.39	0.006
0.1	106.37	0.085
0.01	101.38	0.086
Z factor	0.85	

Compound 64



Activities	
GI50	29.57
TGI	56.63
LC50	83.70
LC100	>100

Concentration, µM	Cell Growth,%	STD
100	-80.12	0.002
10	86.15	0.069
1	97.40	0.017
0.1	101.72	0.072
0.01	99.87	0.060
Z factor	0.86	



	Etoposide
GI50	3.56
TGI	40.18
LC50	87.54
LC100	N/A

Concentration Etoposide, µM	Hela Cell Growth,%	STD
100	-63.16	0.021
10	31.87	0.016
1	57.22	0.047
0.1	99.40	0.014
0.01	103.66	0.005
Z factor	0.95	

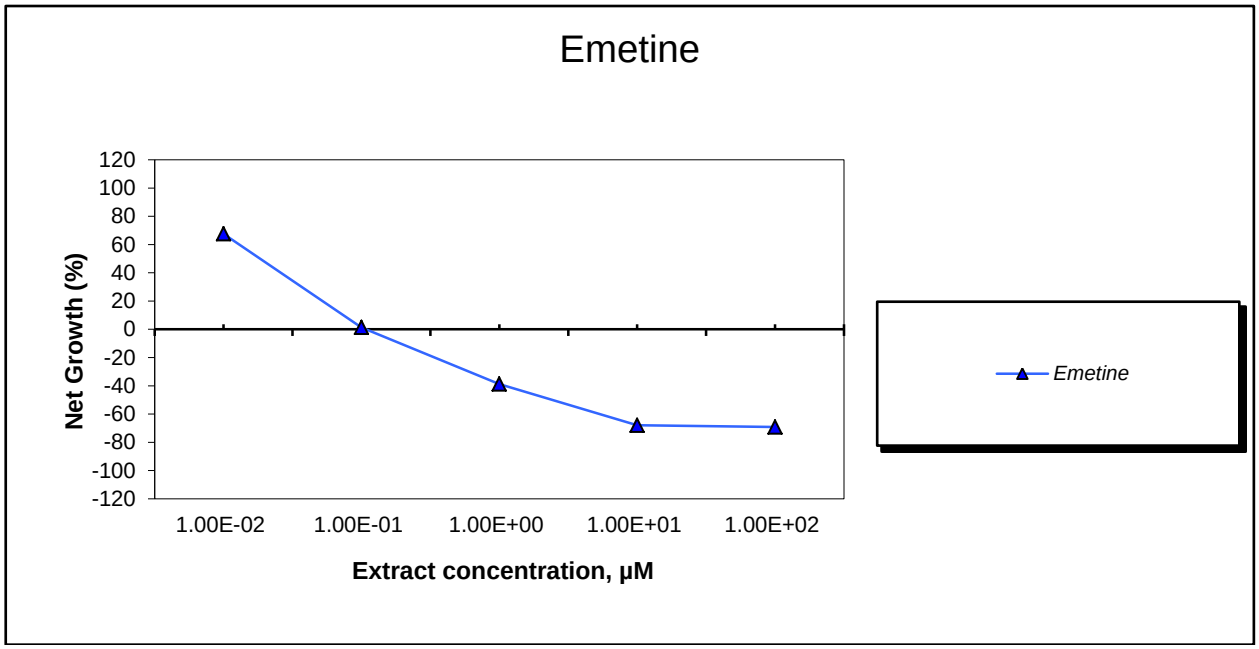
Assay conditions

Samples screened: 6
Test sample concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)

Standard (Emetine) concentration: 100 - 0.01µM (5 x 10-fold serial dilutions)
Read-out: Abs_{540}
Z' Factor : 0.9

Results

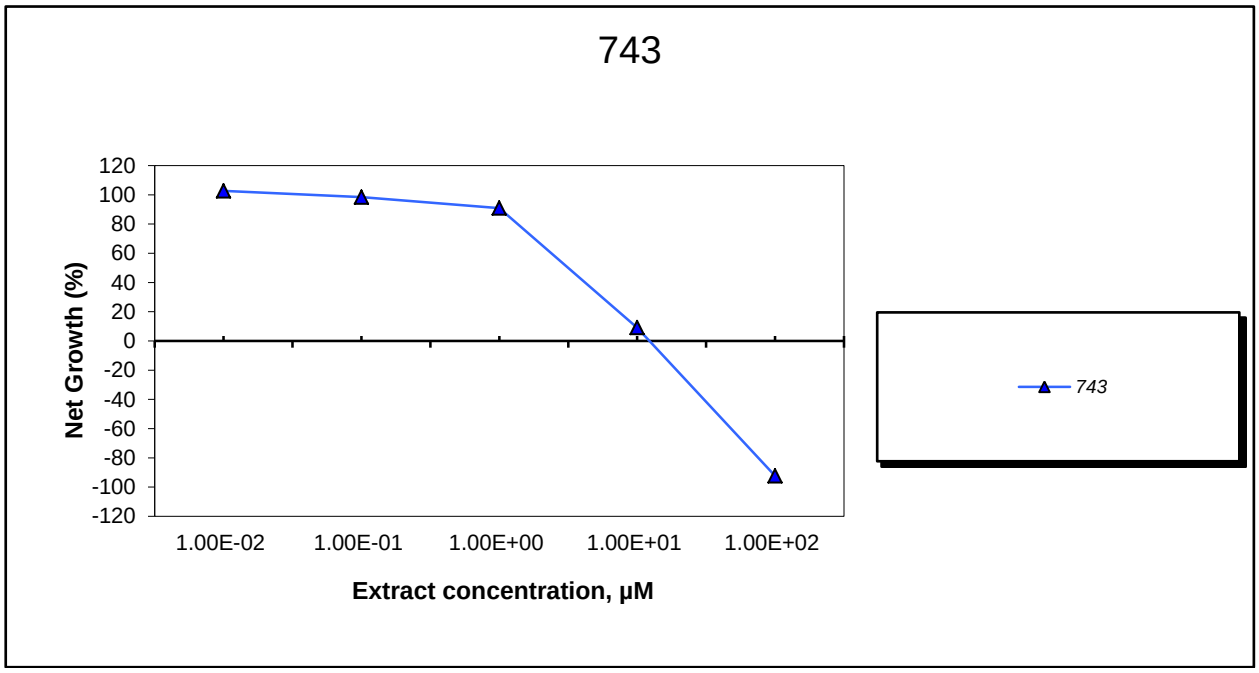
Emetine



Activities	
GI50	0.03
TGI	0.13
LC50	4.46
LC100	>100

Concentration, µM	Cell Growth, %	STD
100	-69.15	0.018
10	-67.95	0.036
1	-38.77	0.012
0.1	1.34	0.006
0.01	67.57	0.048
Z factor	0.92	

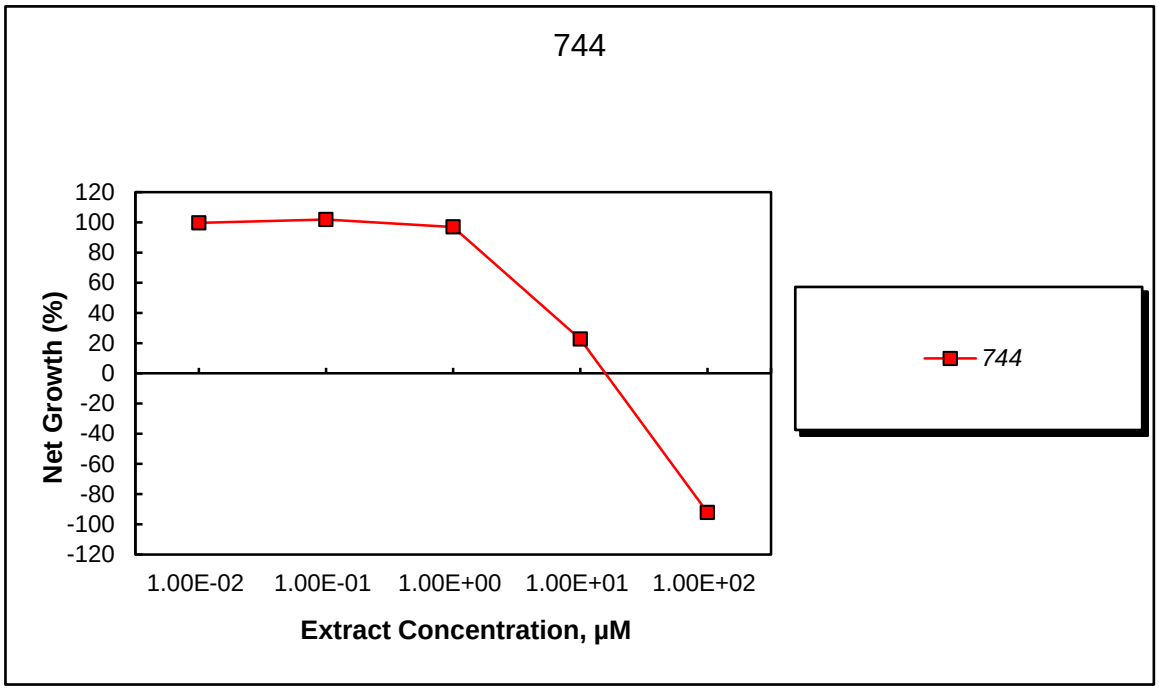
Compound 46



Activities	
GI50	5.50
TGI	18.11
LC50	62.47
LC100	>100

Concentration, µM	Cell Growth,%	STD
100	-92.30	0.001
10	9.14	0.003
1	90.92	0.004
0.1	98.41	0.047
0.01	102.66	0.042
Z factor	0.94	

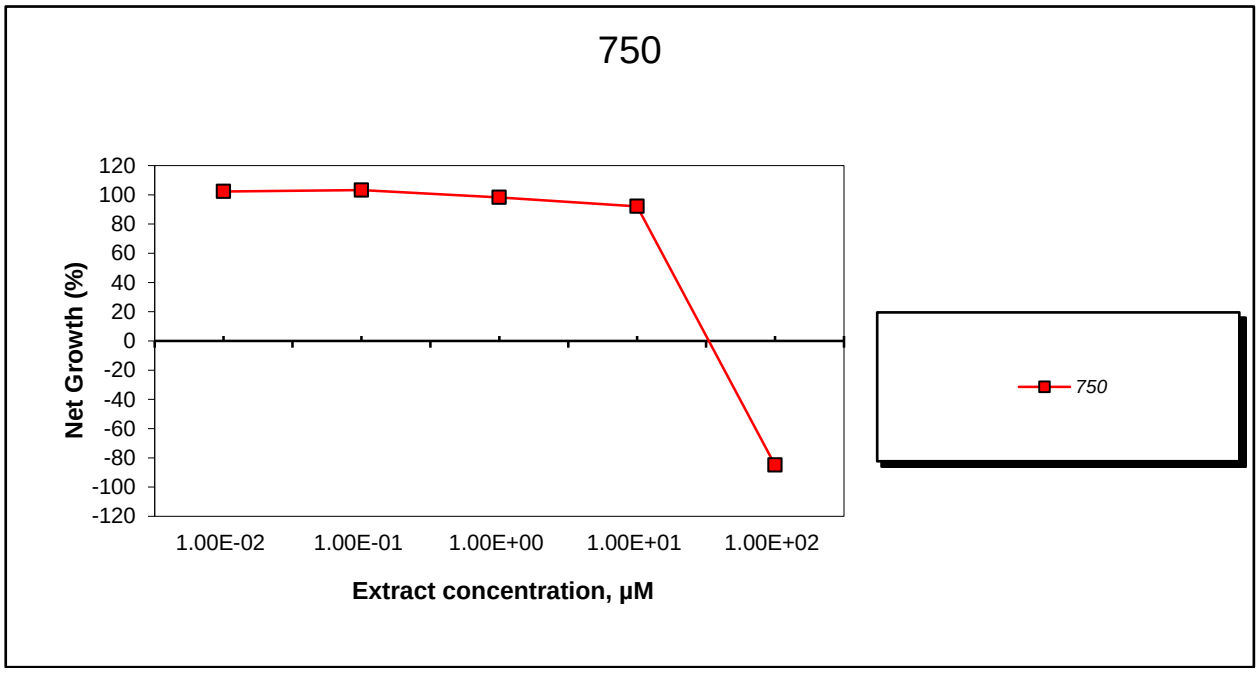
Compound 47



Activities	
GI50	6.68
TGI	27.73
LC50	66.93
LC100	N/A

Concentration, µM	Cell Growth,%	STD
100	-92.18	0.011
10	22.62	0.000
1	96.93	0.057
0.1	101.84	0.033
0.01	99.65	0.008
Z factor	0.88	

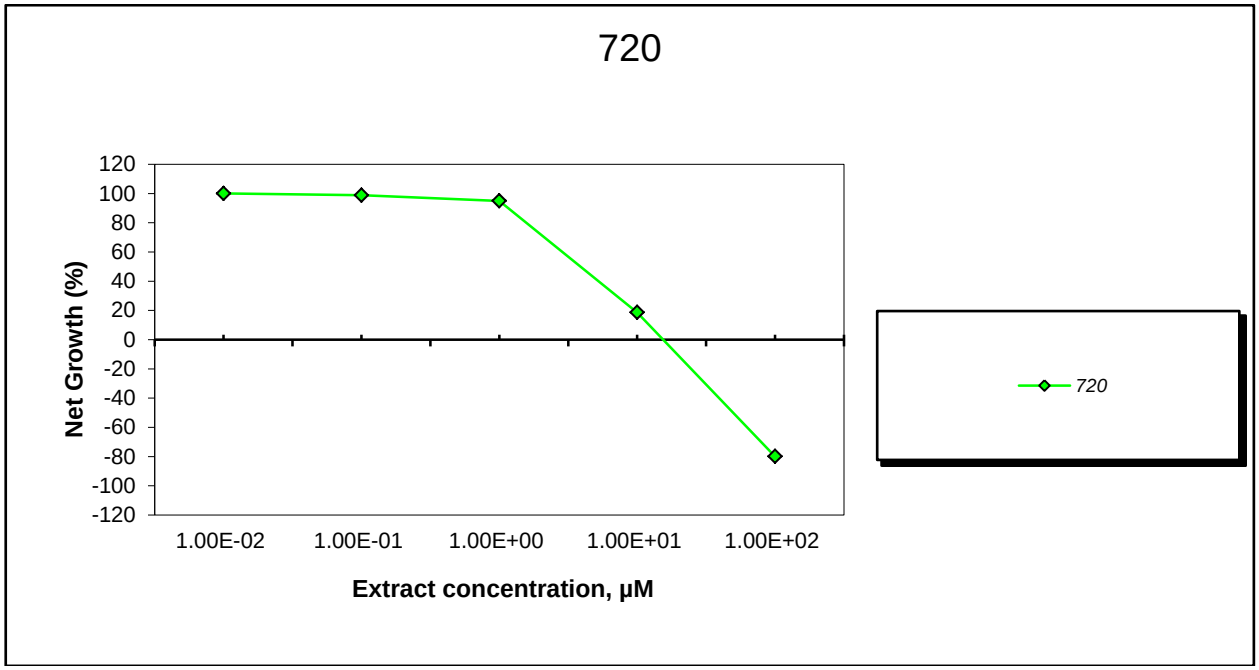
Compound 65



Activities	
GI50	31.40
TGI	56.82
LC50	82.24
LC100	N/A

Concentration, µM	Cell Growth,%	STD
100	-84.93	0.016
10	92.09	0.014
1	98.23	0.008
0.1	103.21	0.014
0.01	102.29	0.038
Z factor	0.90	

Compound 41



Activities	
GI50	6.30
TGI	27.02
LC50	72.70
LC100	N/A

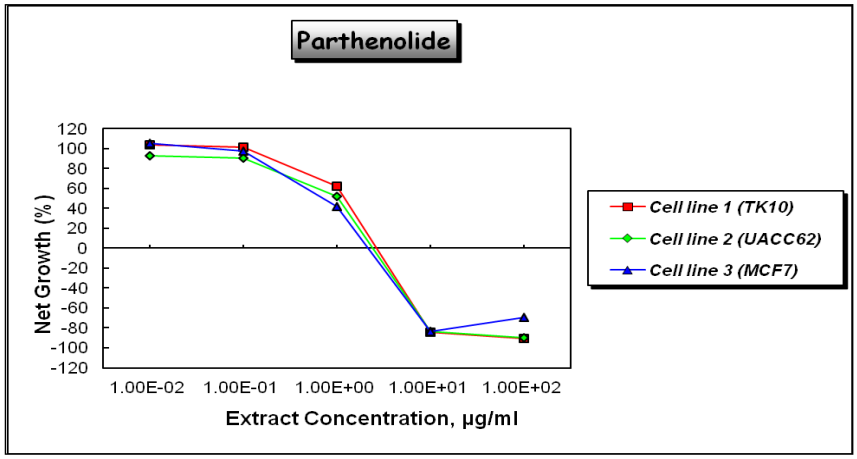
Concentration, µM	Cell Growth,%	STD
100	-79.88	0.025
10	18.63	0.024
1	94.97	0.003
0.1	98.84	0.053
0.01	100.05	0.007
Z factor	0.90	

Assay conditions

Samples screened 5Dose: 30
Test sample concentration: 100 - 0.01µg/ml (5 x 10-fold serial dilutions)
Standard (Parthenolide) concentration: 100 - 0.01µg/ml (5 x 10-fold serial dilutions)
Read-out: Abs_{540}
Z' Factor : 0.7- 0.9

Results

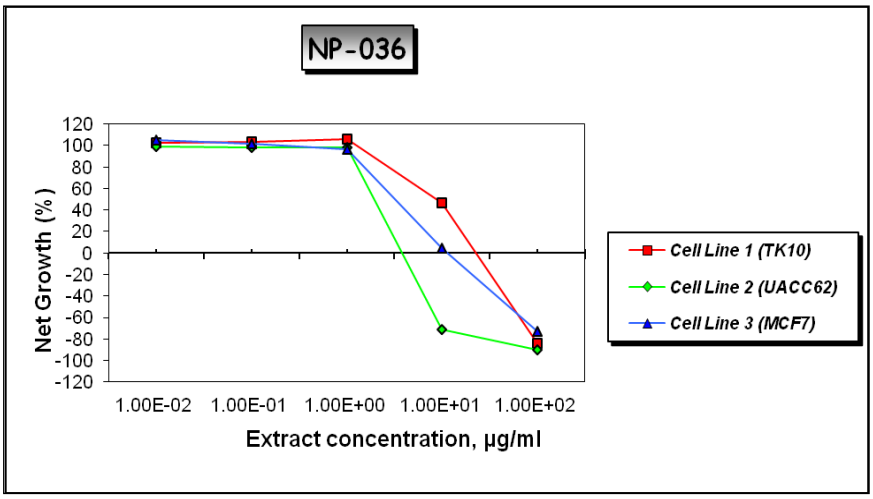
Parthenolide



Activities	TK10	UACC62	MCF7
GI50	1.76	1.15	0.87
TGI	4.82	4.47	4.02
LC50	7.89	7.79	7.60
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-90.87	0.023	-89.81	0.009	-69.42	0.017
10	-84.46	0.197	-83.16	0.030	-83.52	0.006
1	62.42	0.058	52.18	0.057	42.13	0.109
0.1	101.45	0.039	90.56	0.046	97.48	0.045
0.01	103.31	0.072	92.54	0.027	104.94	0.844
Z factor	0.88		0.91		0.86	

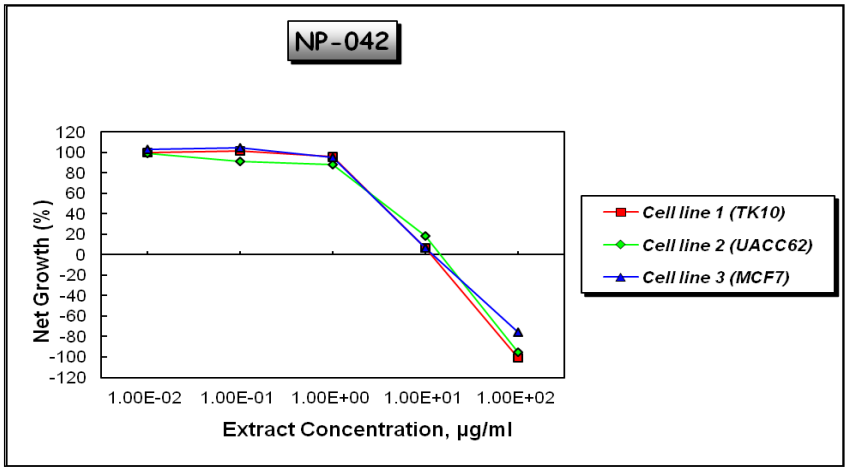
Compound 73



Activities	TK10	UACC62	MCF7
GI50	9.52	3.57	5.56
TGI	42.21	6.22	15.05
LC50	76.56	8.86	73.40
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-84.12	0.002	-89.89	0.033	-72.79	0.002
10	46.88	0.017	-71.46	0.047	4.33	0.074
1	105.93	0.019	98.50	0.076	96.83	0.139
0.1	102.96	0.032	98.19	0.087	101.98	0.141
0.01	102.81	0.007	99.37	0.043	105.32	0.031
Z factor	0.93		0.78		0.63	

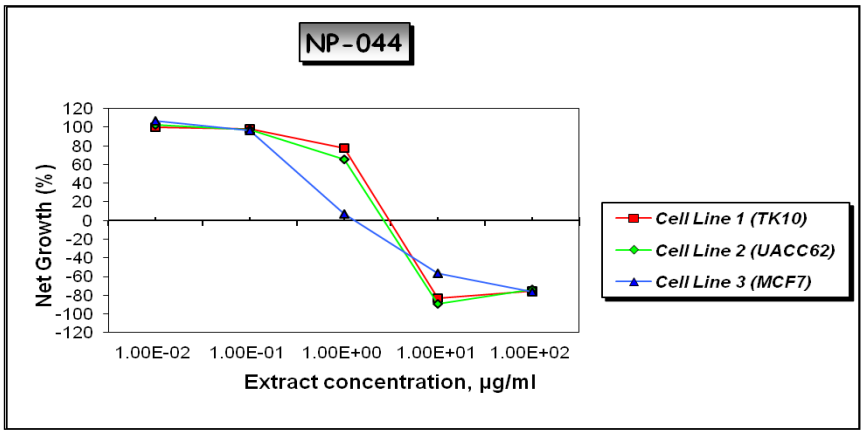
Compound 55



Activities	TK10	UACC62	MCF7
GI50	5.62	5.88	5.55
TGI	15.55	24.36	16.97
LC50	57.34	64.04	71.94
LC100	99.14	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-101.03	0.004	-95.31	0.004	-75.53	0.001
10	6.64	0.027	18.09	0.041	6.34	0.015
1	95.75	0.042	87.85	0.065	94.67	0.040
0.1	101.15	0.061	91.11	0.125	104.16	0.047
0.01	99.82	0.016	98.94	0.067	103.18	0.941
Z factor	0.93		0.78		0.63	

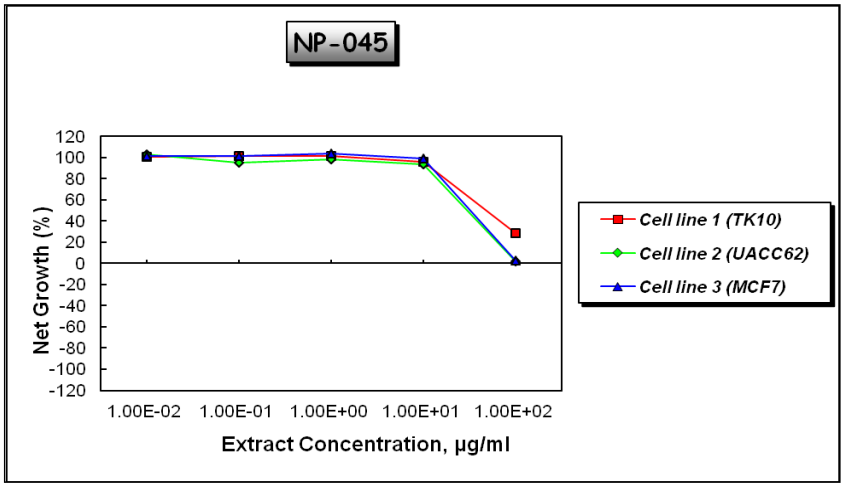
Compound 56



Activities	TK10	UACC62	MCF7
GI50	2.56	1.91	0.57
TGI	5.36	4.81	1.99
LC50	8.15	7.72	9.11
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-75.02	0.017	-74.05	0.047	-76.06	0.007
10	-83.03	0.040	-89.22	0.032	-56.25	0.007
1	77.86	0.125	65.63	0.058	6.98	0.034
0.1	98.51	0.005	97.26	0.040	96.22	0.046
0.01	100.11	0.000	102.30	0.099	106.60	0.065
Z factor	0.89		0.83		0.59	

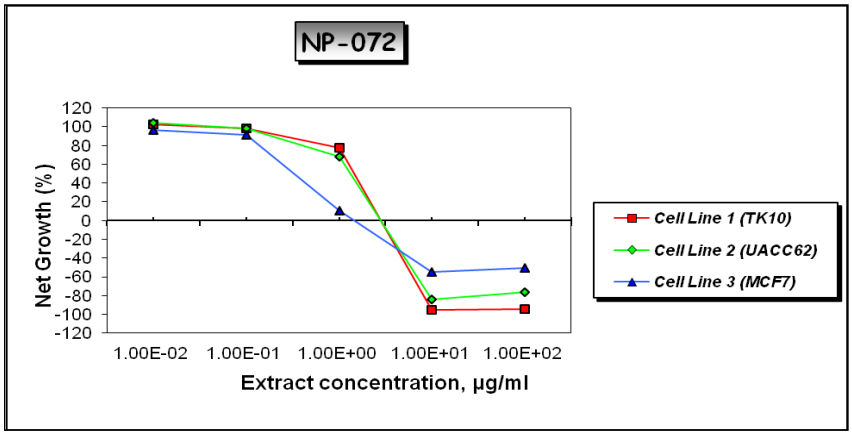
Compound 62



Activities	TK10	UACC62	MCF7
GI50	70.85	52.58	55.81
TGI	>100	>100	>100
LC50	>100	>100	>100
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	28.22	0.006	1.97	0.044	2.67	0.013
10	95.47	0.067	93.13	0.008	99.06	0.062
1	101.10	0.068	98.03	0.102	103.58	0.099
0.1	101.23	0.055	94.81	0.016	101.16	0.177
0.01	100.70	0.023	103.19	0.074	101.69	0.922
Z factor	0.89		0.83		0.59	

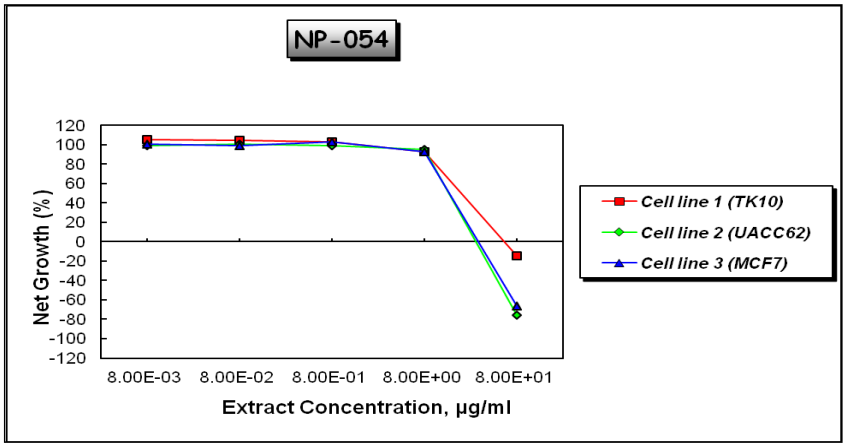
Compound 57



Activities	TK10	UACC62	MCF7
GI50	2.44	2.09	0.56
TGI	5.05	5.05	2.45
LC50	7.65	8.00	9.34
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-93.99	0.031	-76.07	0.001	-50.11	0.033
10	-95.17	0.006	-83.79	0.041	-54.78	0.008
1	77.76	0.100	68.53	0.019	10.49	0.055
0.1	97.83	0.045	98.36	0.031	91.37	0.072
0.01	102.83	0.041	104.19	0.006	96.72	0.050
Z factor	0.76		0.79		0.92	

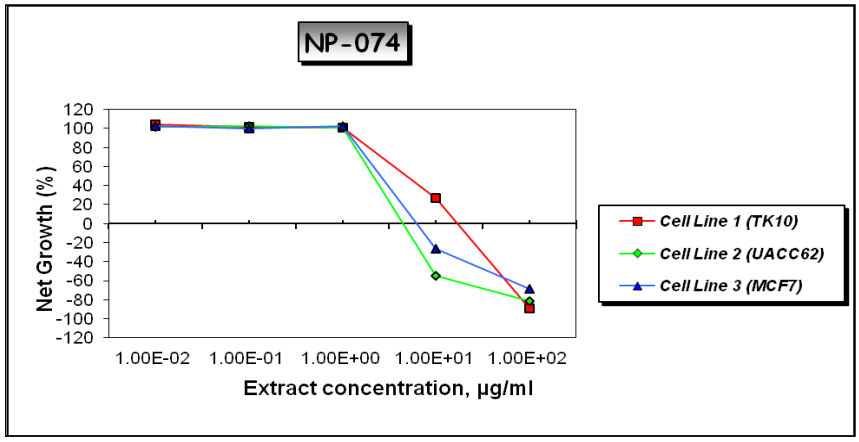
Compound 61



Activities	TK10	UACC62	MCF7
GI50	36.58	26.96	27.30
TGI	70.31	48.09	50.02
LC50	>100	69.22	72.75
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
80	-14.36	0.009	-75.50	0.025	-65.96	0.016
8	92.37	0.016	94.87	0.048	92.46	0.082
0.8	102.87	0.038	98.94	0.030	102.52	0.049
0.08	104.29	0.057	100.33	0.038	98.63	0.128
0.008	104.99	0.076	98.88	0.004	100.55	0.927
Z factor	0.76		0.79		0.92	

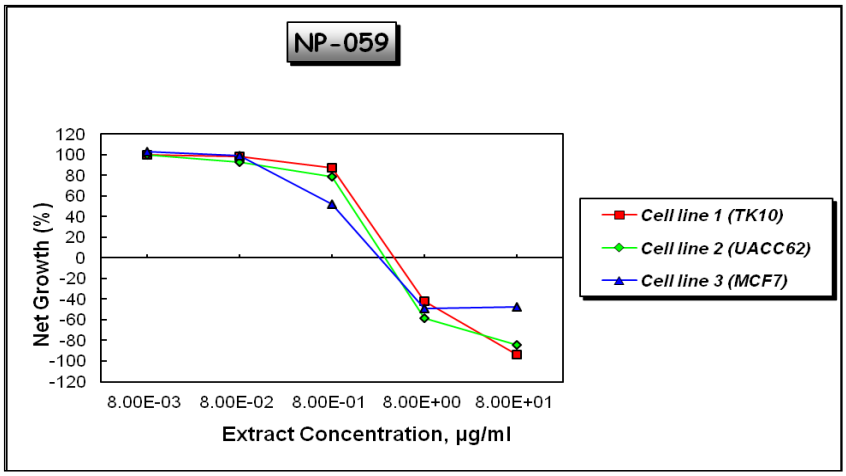
Compound 68



Activities	TK10	UACC62	MCF7
GI50	7.14	3.95	4.67
TGI	30.63	6.84	8.18
LC50	69.47	9.73	61.20
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-89.30	0.005	-81.17	0.011	-68.18	0.027
10	26.55	0.084	-54.73	0.024	-26.01	0.065
1	100.38	0.057	101.19	0.037	102.35	0.016
0.1	102.06	0.044	102.74	0.060	99.94	0.024
0.01	103.97	0.132	101.80	0.043	102.71	0.060
Z factor	0.79		0.80		0.88	

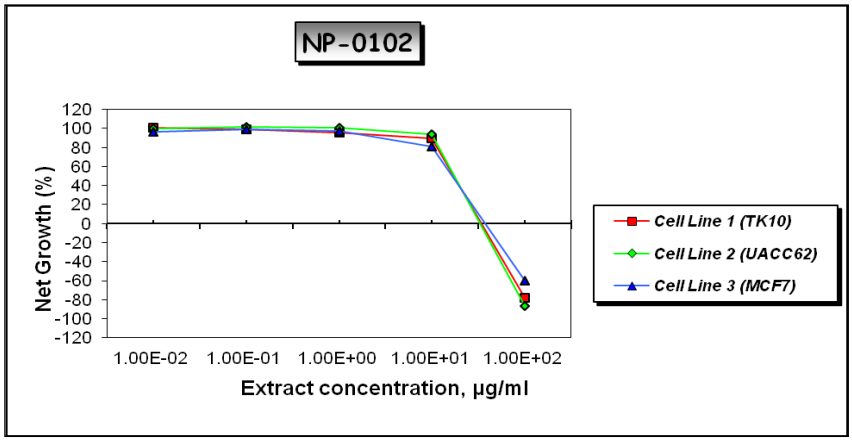
Compound 54



Activities	TK10	UACC62	MCF7
GI50	2.89	2.30	0.92
TGI	5.68	4.93	4.49
LC50	19.48	7.56	>100
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
80	-93.64	0.019	-84.10	0.036	-47.41	0.030
8	-41.72	0.010	-58.30	0.043	-49.07	0.016
0.8	87.58	0.105	78.44	0.000	51.73	0.031
0.08	98.11	0.107	92.74	0.120	99.31	0.049
0.008	100.00	0.110	99.85	0.080	102.59	0.981
Z factor	0.79		0.80		0.88	

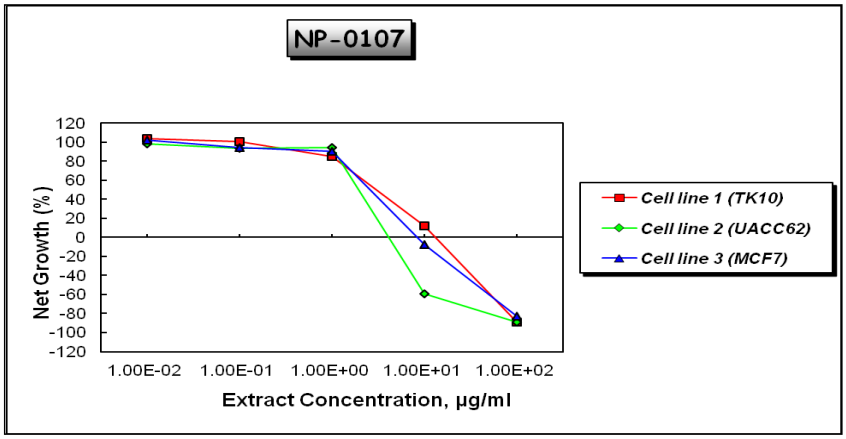
Compound 66



Activities	TK10	UACC62	MCF7
GI50	31.24	31.84	29.68
TGI	58.14	56.74	61.66
LC50	85.04	81.65	93.63
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-77.80	0.004	-86.84	0.035	-59.95	0.018
10	89.48	0.024	93.84	0.044	80.77	0.012
1	95.72	0.040	100.67	0.081	97.33	0.034
0.1	99.10	0.087	101.86	0.048	98.88	0.057
0.01	100.65	0.100	99.53	0.000	96.78	0.046
Z factor	0.79		0.82		0.61	

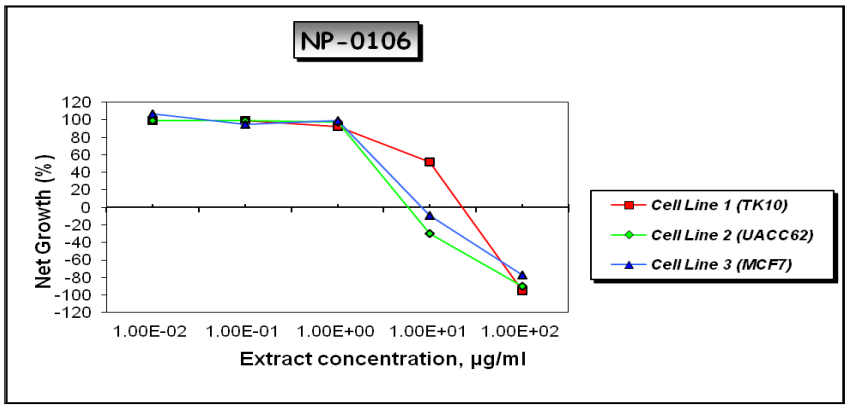
Compound 75



Activities	TK10	UACC62	MCF7
GI50	5.31	3.60	4.71
TGI	20.91	6.53	9.29
LC50	65.32	9.46	60.75
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-89.05	0.005	-88.85	0.004	-82.69	0.008
10	12.28	0.031	-59.17	0.059	-7.72	0.012
1	84.63	0.045	94.31	0.056	90.50	0.070
0.1	100.54	0.038	93.22	0.051	93.98	0.124
0.01	104.04	0.061	98.31	0.102	102.41	0.981
Z factor	0.79		0.82		0.61	

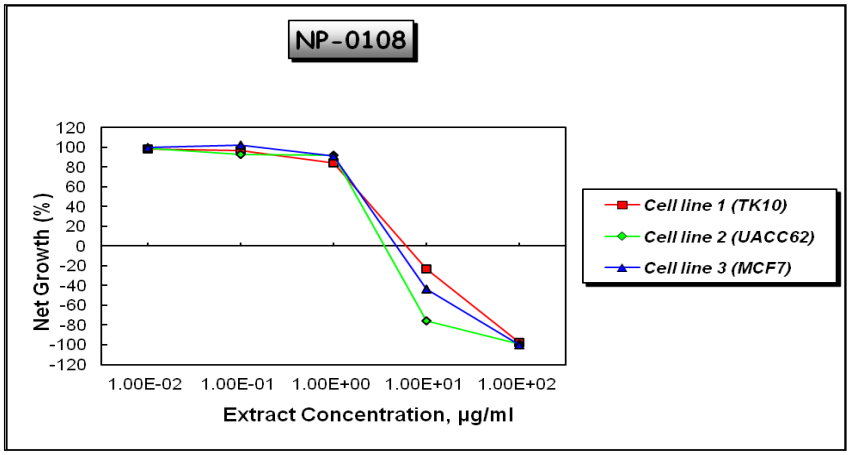
Compound 74



Activities	TK10	UACC62	MCF7
GI50	11.20	4.33	5.11
TGI	41.82	7.86	9.27
LC50	72.44	39.70	64.21
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-95.00	0.015	-90.19	0.002	-77.18	0.003
10	51.96	0.073	-30.21	0.025	-8.82	0.045
1	91.86	0.127	97.00	0.011	99.48	0.019
0.1	99.46	0.157	98.70	0.031	94.39	0.035
0.01	98.65	0.145	99.22	0.047	106.41	0.007
Z factor	0.71		0.92		0.65	

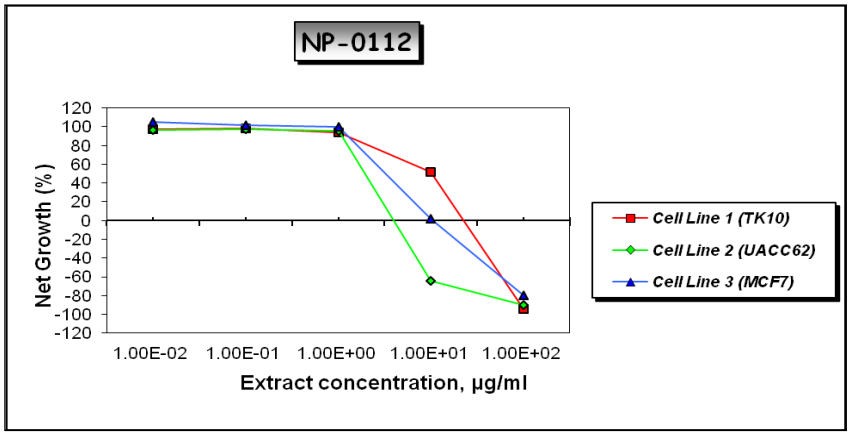
Compound 76



Activities	TK10	UACC62	MCF7
GI50	3.84	3.26	3.75
TGI	8.06	5.94	7.09
LC50	42.66	8.62	20.16
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-97.42	0.011	-99.25	0.002	-99.72	0.002
10	-22.99	0.120	-75.75	0.048	-43.67	0.009
1	83.72	0.154	92.27	0.048	91.24	0.003
0.1	96.32	0.176	93.06	0.013	101.91	0.205
0.01	98.25	0.156	99.16	0.029	99.67	0.873
Z factor	0.71		0.92		0.65	

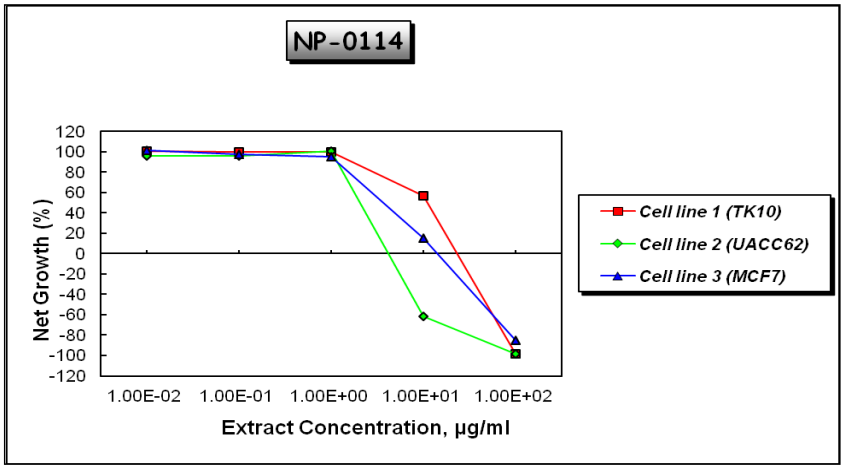
Compound 77



Activities	TK10	UACC62	MCF7
GI50	10.92	3.55	5.60
TGI	41.73	6.37	12.52
LC50	72.54	9.18	67.67
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-94.56	0.011	-90.41	0.045	-79.31	0.002
10	51.50	0.004	-64.52	0.100	2.28	0.083
1	94.02	0.017	95.23	0.064	99.81	0.011
0.1	98.56	0.006	97.28	0.026	101.26	0.076
0.01	97.68	0.030	96.26	0.025	105.05	0.089
Z factor	0.93		0.86		0.72	

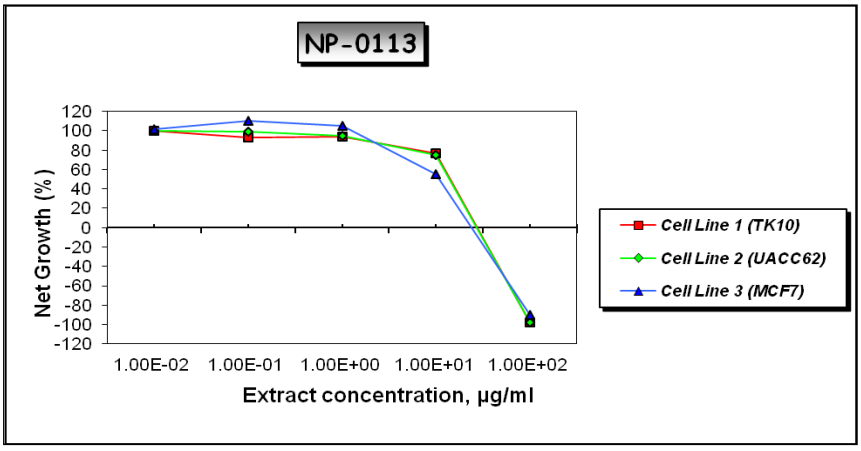
Compound 79



Activities	TK10	UACC62	MCF7
GI50	13.89	3.80	6.06
TGI	42.88	6.58	23.41
LC50	71.88	9.37	68.58
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-98.49	0.001	-98.48	0.006	-84.78	0.010
10	56.71	0.010	-61.32	0.059	14.84	0.025
1	99.45	0.061	100.24	0.035	95.12	0.074
0.1	99.91	0.045	95.64	0.028	97.23	0.020
0.01	100.82	0.022	95.98	0.001	101.54	0.860
Z factor	0.93		0.86		0.72	

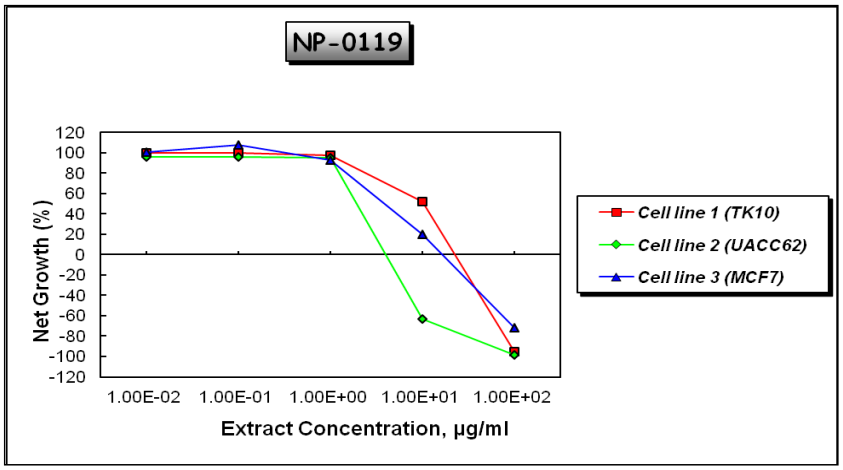
Compound 78



Activities	TK10	UACC62	MCF7
GI50	23.67	23.09	13.10
TGI	49.47	49.12	44.16
LC50	75.26	75.16	75.22
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-97.95	0.015	-97.70	0.014	-89.88	0.010
10	76.49	0.000	75.13	0.099	54.99	0.027
1	94.30	0.040	94.98	0.036	105.14	0.008
0.1	92.65	0.006	98.91	0.025	109.92	0.004
0.01	99.76	0.007	100.00	0.011	101.38	0.002
Z factor	0.89		0.80		0.75	

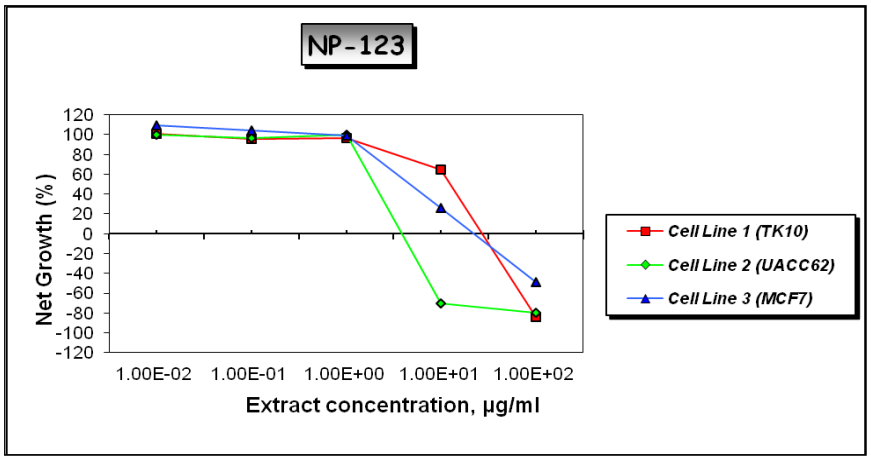
Compound 72



Activities	TK10	UACC62	MCF7
GI50	11.07	3.57	6.27
TGI	41.75	6.42	29.24
LC50	72.43	9.26	78.48
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-94.94	0.017	-98.69	0.006	-71.85	0.006
10	51.74	0.018	-62.99	0.030	19.53	0.019
1	97.59	0.015	95.25	0.030	92.99	0.042
0.1	99.65	0.026	95.45	0.058	107.32	0.074
0.01	99.87	0.001	95.83	0.033	100.15	0.841
Z factor	0.89		0.80		0.75	

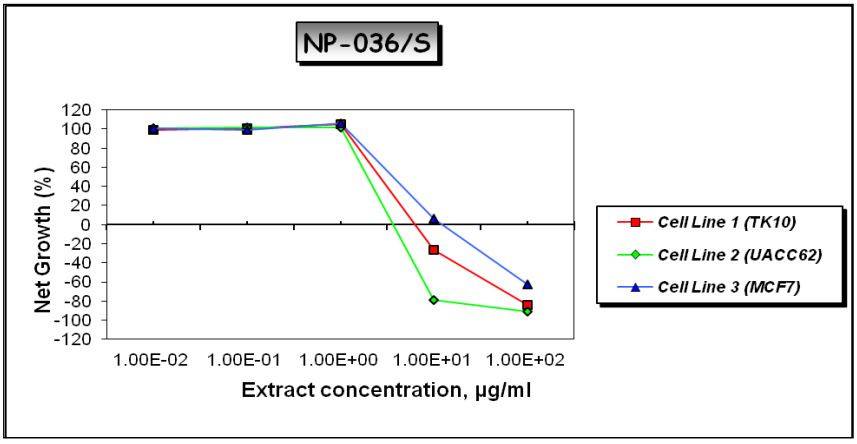
Compound 95



Activities	TK10	UACC62	MCF7
GI50	19.02	3.63	7.03
TGI	49.30	6.27	41.05
LC50	79.58	8.92	>100
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-83.71	0.007	-80.11	0.004	-48.83	0.013
10	64.89	0.008	-70.37	0.007	25.72	0.139
1	96.85	0.036	99.58	0.052	99.26	0.128
0.1	95.83	0.047	96.26	0.003	104.30	0.042
0.01	100.99	0.015	100.03	0.011	108.99	0.223
Z factor	0.77		0.91		0.94	

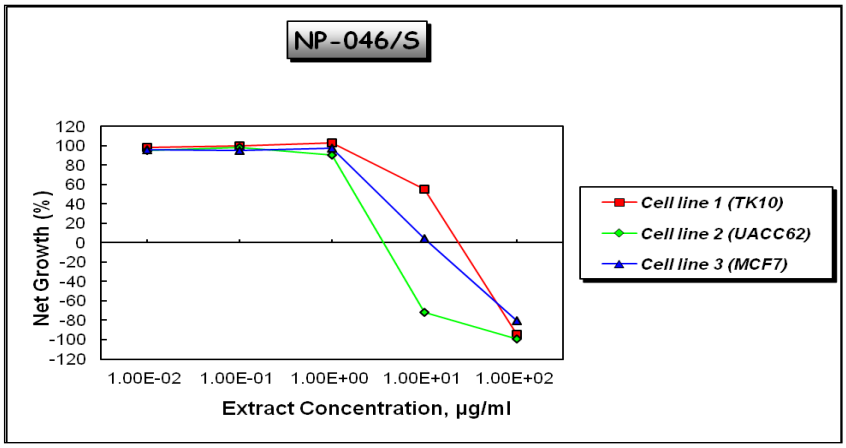
Compound 82



Activities	TK10	UACC62	MCF7
GI50	4.76	3.57	6.06
TGI	8.20	6.06	18.72
LC50	47.25	8.55	84.18
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-83.73	0.039	-90.51	0.010	-62.08	0.004
10	-26.18	0.022	-79.22	0.005	6.66	0.024
1	104.71	0.086	101.69	0.020	105.70	0.080
0.1	100.41	0.040	101.59	0.031	98.78	0.083
0.01	98.81	0.141	100.84	0.002	100.59	0.021
Z factor	-83.73	0.039	-90.51	0.010	-62.08	0.004

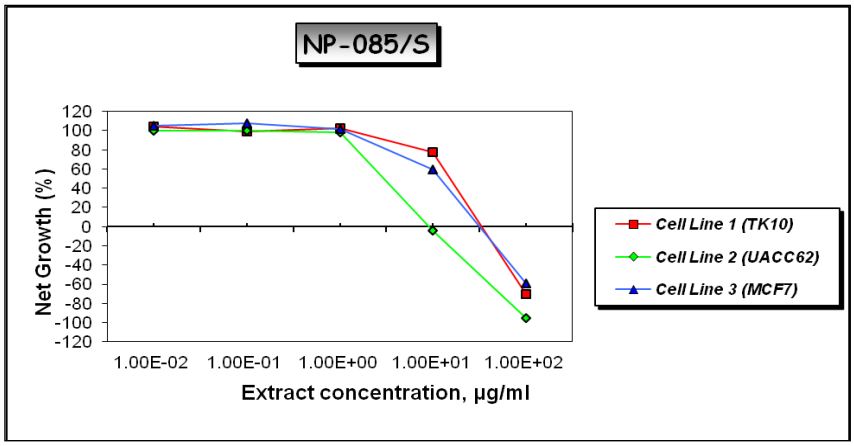
Compound 81



Activities	TK10	UACC62	MCF7
GI50	13.21	3.25	5.58
TGI	43.28	6.02	14.82
LC50	73.34	8.80	67.97
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-94.33	0.036	-98.97	0.002	-80.13	0.015
10	55.34	0.039	-71.70	0.020	4.53	0.025
1	103.26	0.081	90.50	0.045	97.12	0.006
0.1	99.76	0.004	97.91	0.041	94.76	0.171
0.01	98.06	0.079	95.26	0.069	95.91	0.916
Z factor	0.76		0.87		0.83	

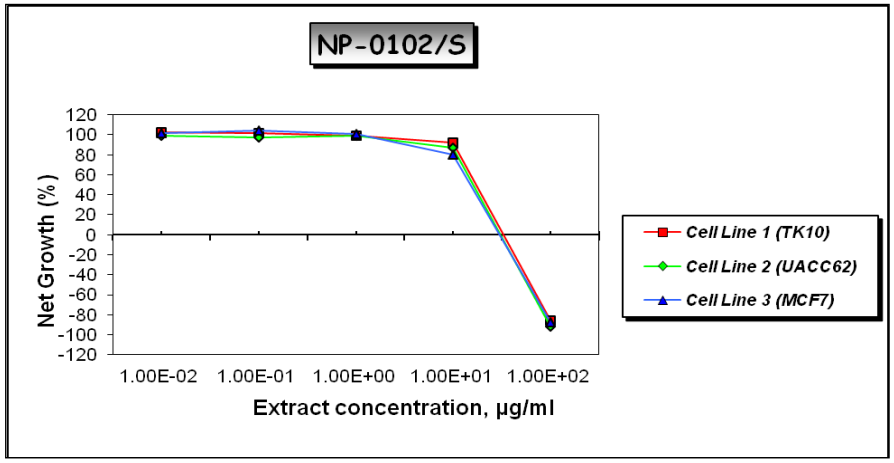
Compound 84



Activities	TK10	UACC62	MCF7
GI50	26.79	5.24	16.94
TGI	57.21	9.62	54.95
LC50	87.63	55.45	92.96
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-70.33	0.004	-94.76	0.003	-59.26	0.000
10	77.60	0.057	-4.32	0.032	59.13	0.078
1	102.88	0.066	98.50	0.082	101.76	0.043
0.1	98.88	0.075	100.11	0.110	107.46	0.065
0.01	104.42	0.032	99.50	0.113	104.96	0.040
Z factor	0.79		0.75		0.78	

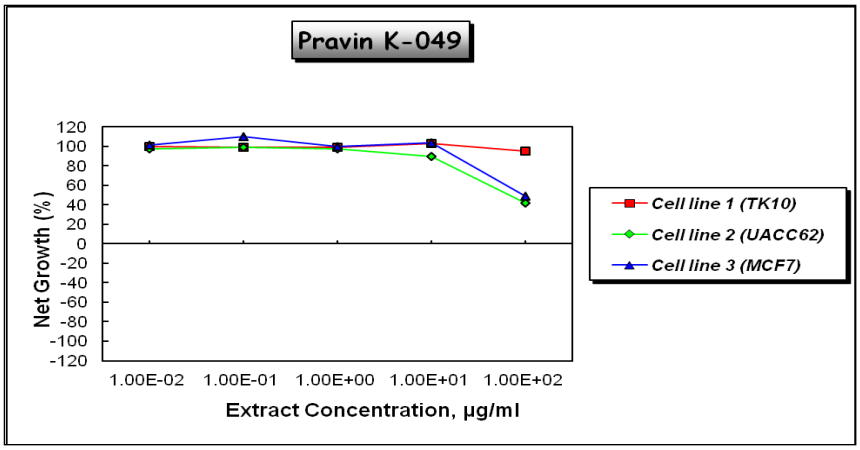
Compound 83



Activities	TK10	UACC62	MCF7
GI50	31.40	28.51	26.05
TGI	56.73	53.73	52.92
LC50	82.06	78.94	79.80
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-85.42	0.028	-91.77	0.013	-87.60	0.001
10	92.25	0.074	86.72	0.002	79.87	0.085
1	98.91	0.093	99.43	0.030	100.41	0.055
0.1	101.42	0.091	97.12	0.063	104.16	0.051
0.01	102.30	0.070	98.80	0.026	101.74	0.003
Z factor	0.76		0.86		0.95	

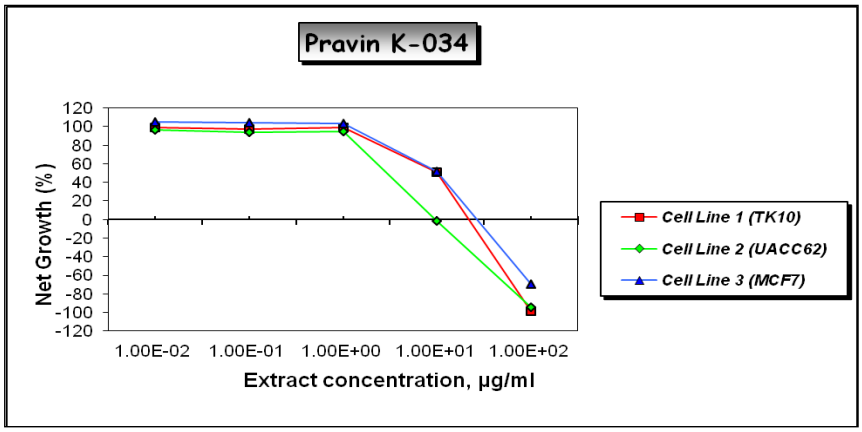
Compound 85



Activities	TK10	UACC62	MCF7
GI50	>100	84.79	98.45
TGI	>100	>100	>100
LC50	>100	>100	>100
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	94.74	0.066	41.92	0.013	49.07	0.094
10	102.70	0.127	89.72	0.068	103.45	0.012
1	98.94	0.131	97.71	0.032	100.07	0.054
0.1	99.24	0.078	99.29	0.040	109.72	0.007
0.01	99.49	0.106	97.06	0.013	100.94	0.885
Z factor	0.76		0.86		0.95	

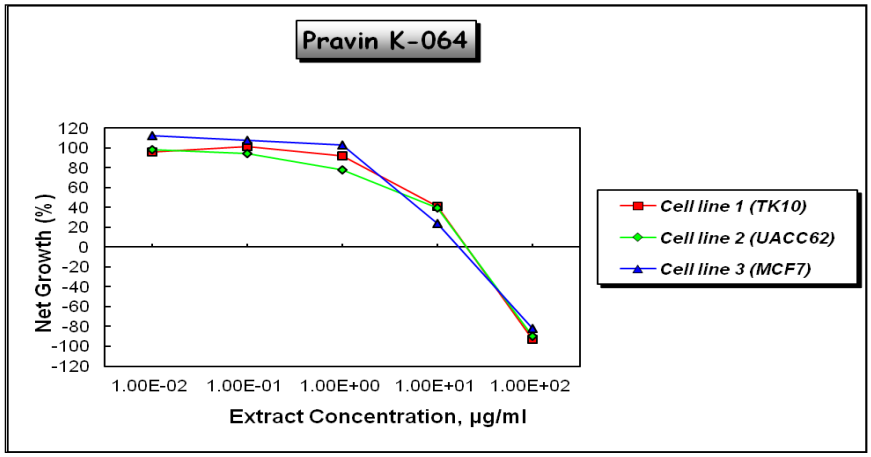
Compound 89



Activities	TK10	UACC62	MCF7
GI50	10.32	5.20	11.50
TGI	40.48	9.88	48.48
LC50	70.64	57.02	85.45
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-98.68	0.002	-94.49	0.006	-69.68	0.008
10	50.54	0.048	-1.33	0.461	52.03	0.088
1	99.24	0.062	94.91	0.031	102.94	0.091
0.1	97.60	0.041	93.62	0.028	104.13	0.071
0.01	99.02	0.022	96.88	0.004	104.72	0.033
Z factor	0.87		0.86		0.89	

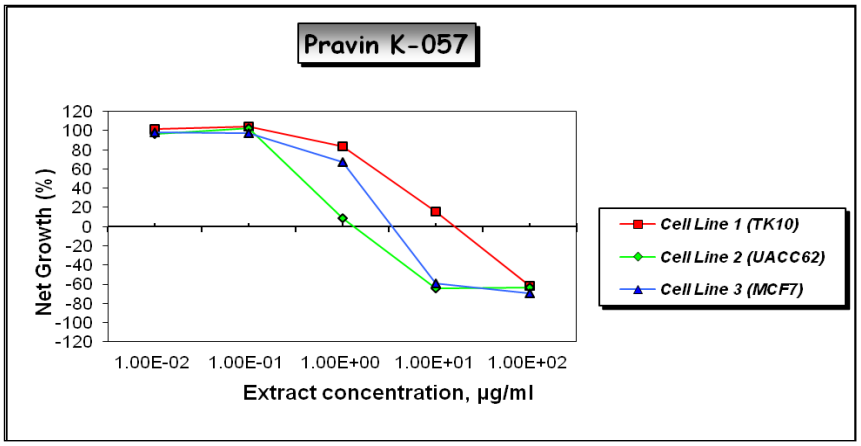
Compound 92



Activities	TK10	UACC62	MCF7
GI50	8.40	7.47	7.02
TGI	37.61	37.42	30.41
LC50	71.24	72.36	73.06
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-92.76	0.006	-89.57	0.003	-81.59	0.004
10	41.04	0.021	39.25	0.035	23.93	0.033
1	91.57	0.000	77.51	0.076	102.66	0.107
0.1	101.26	0.018	94.32	0.058	107.33	0.021
0.01	95.48	0.007	98.08	0.025	111.92	0.977
Z factor	0.87		0.86		0.89	

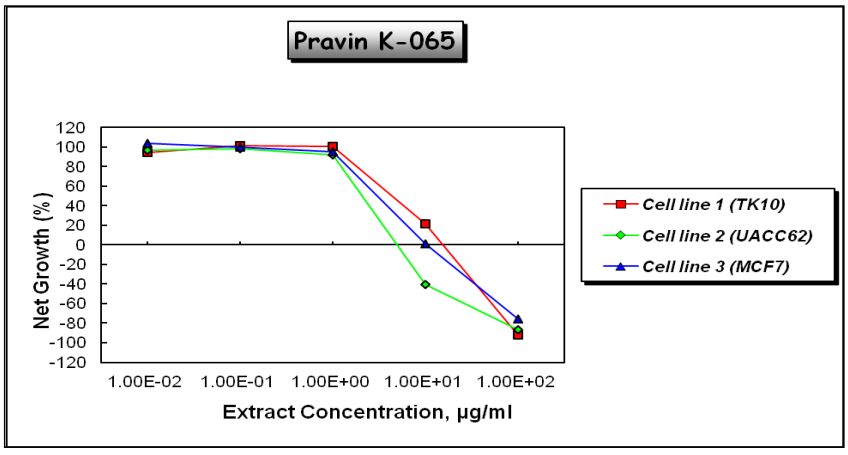
Compound 93



Activities	TK10	UACC62	MCF7
GI50	5.45	0.61	2.23
TGI	27.78	2.11	5.80
LC50	85.96	8.26	9.37
LC100	>100	>100	>100

Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-62.06	0.013	-63.35	0.037	-69.15	0.000
10	15.27	0.035	-64.18	0.069	-58.89	0.003
1	83.93	0.008	9.03	0.067	67.22	0.020
0.1	104.48	0.043	102.90	0.037	97.34	0.028
0.01	101.48	0.051	96.33	0.091	98.01	0.204
Z factor	0.81		0.93		0.67	

Compound 71



Activities	TK10	UACC62	MCF7
GI50	6.75	3.86	5.33
TGI	27.07	7.24	11.58
LC50	66.54	28.43	69.69
LC100	>100	>100	>100

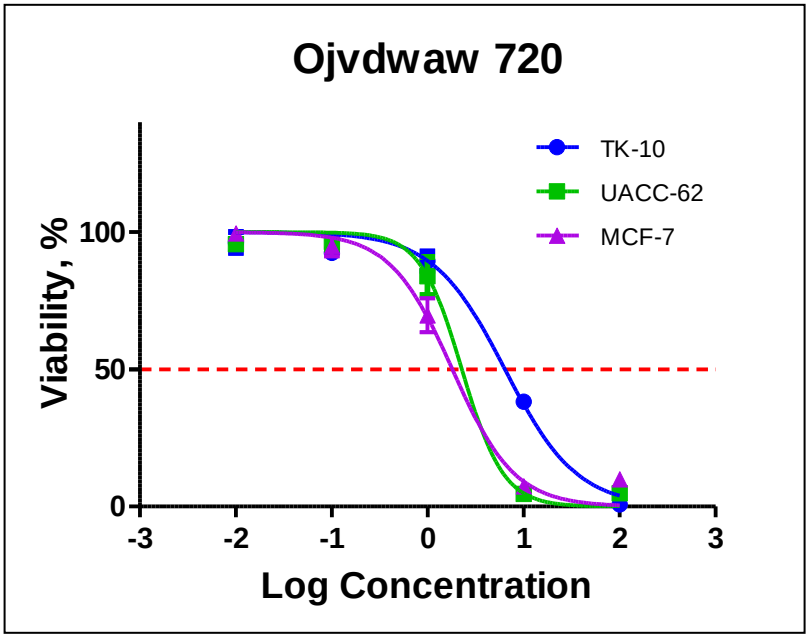
Conc, µg/ml	Cell Growth,% TK10	STD	Cell Growth,% UACC62	STD	Cell Growth, % MCF7	STD
100	-92.38	0.031	-86.29	0.045	-76.08	0.006
10	21.62	0.053	-40.65	0.060	1.36	0.025
1	100.20	0.102	92.13	0.062	95.04	0.047
0.1	101.40	0.088	98.07	0.058	100.07	0.060
0.01	94.21	0.008	96.26	0.061	103.38	0.934
Z factor	0.81		0.93		0.67	

1.4 Cancer Screening results – IC_{50} values

The following tables and graphs represent the IC_{50} values calculated from the TGI values for all three cancer cell lines. These IC_{50} values can not be directly compared to the IC_{50} values obtained for the antimalarial bioactivity.

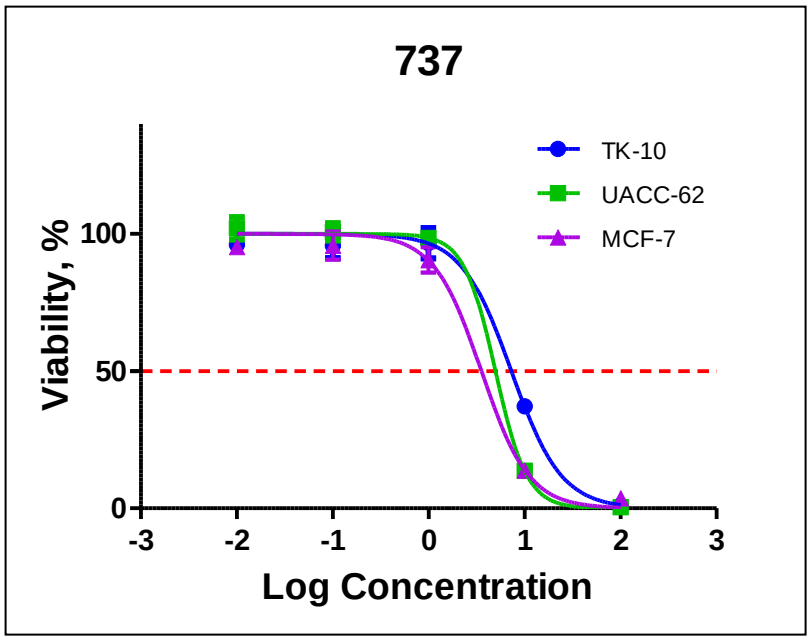
Compound 71

	TK-10	UACC-62	MCF-7
IC50,µM	6.40	2.28	1.81

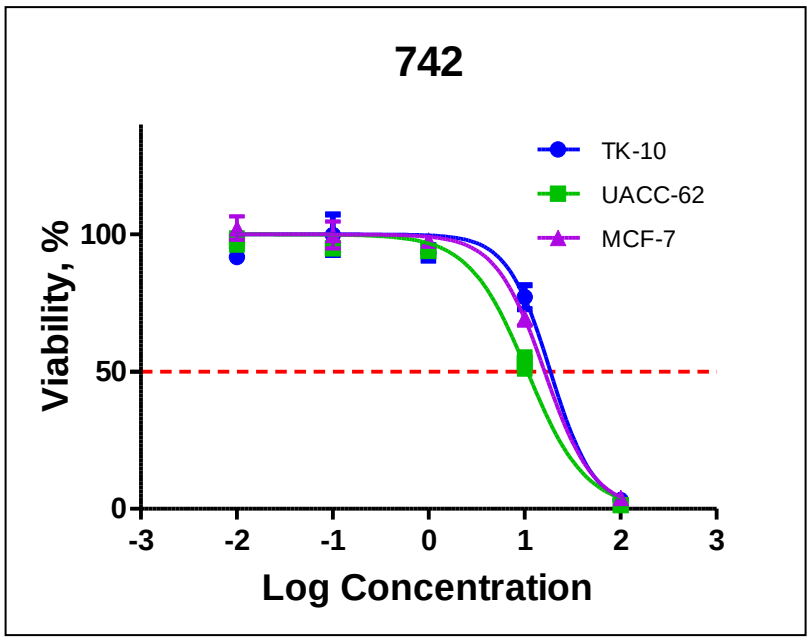


Compound 71

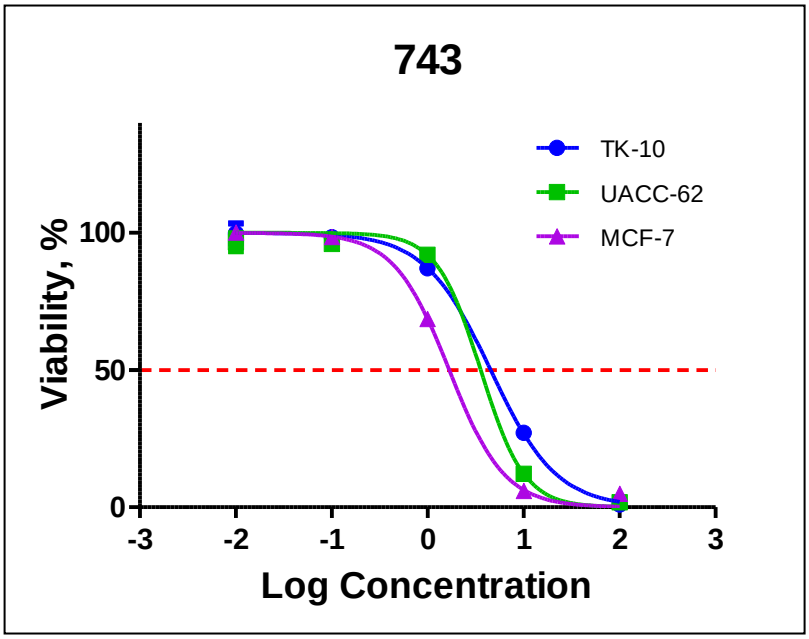
	TK-10	UACC-62	MCF-7
IC50, µM	7.30	4.98	3.55



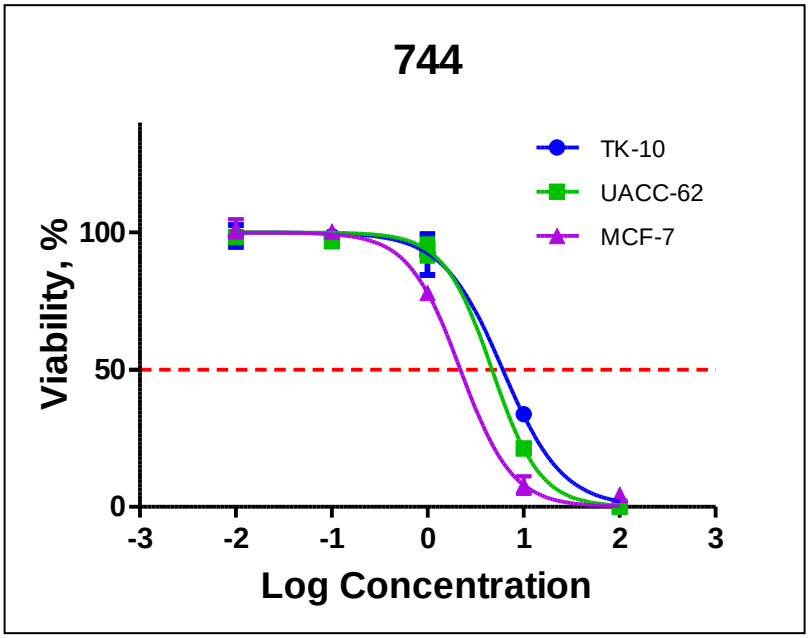
	TK-10	UACC-62	MCF-7
IC50, µM	18.65	10.68	16.19



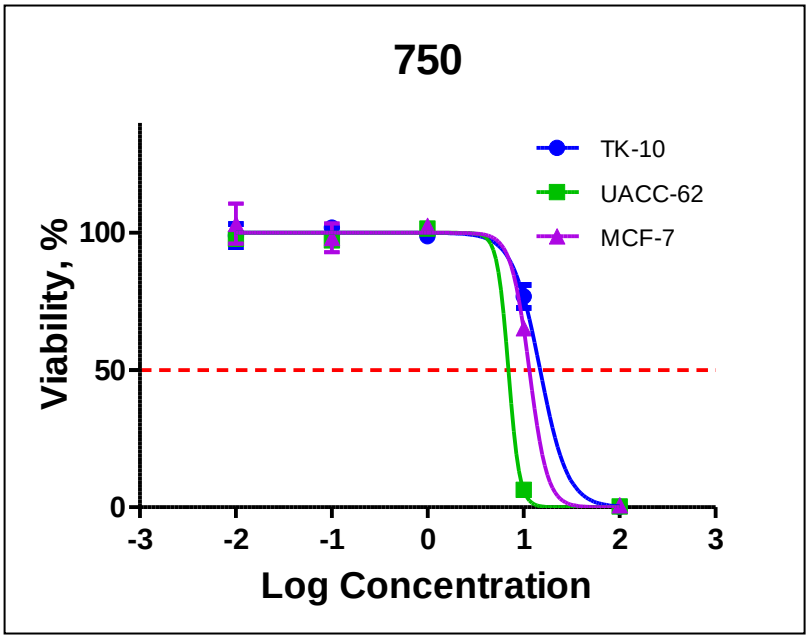
	TK-10	UACC-62	MCF-7
IC50, µM	4.54	3.57	1.68



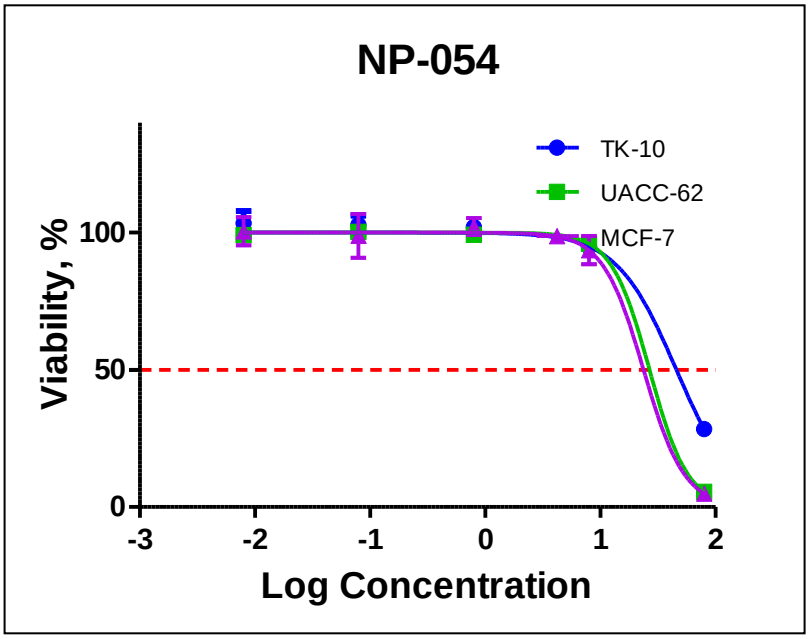
	TK-10	UACC-62	MCF-7
IC50, µM	6.078	4.69	2.197



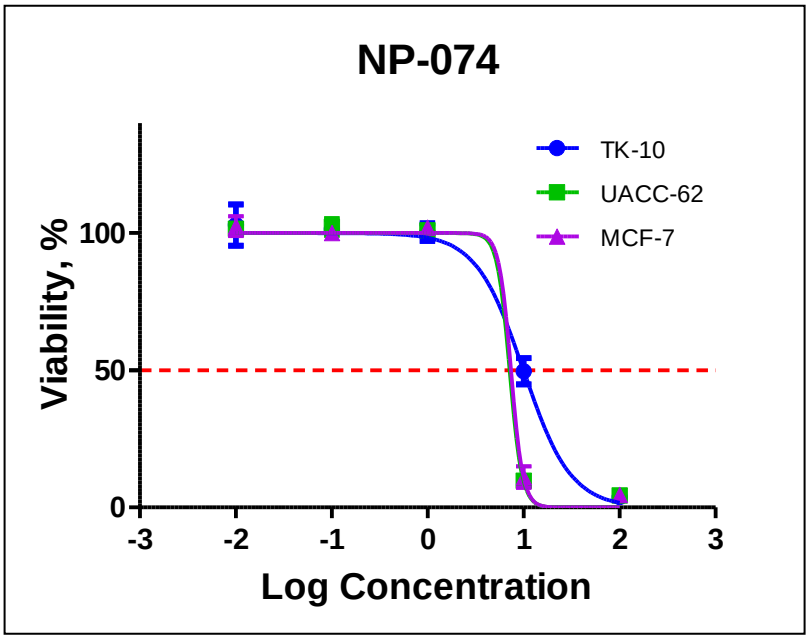
	TK-10	UACC-62	MCF-7
IC50, µM	14.89	6.967	11.47



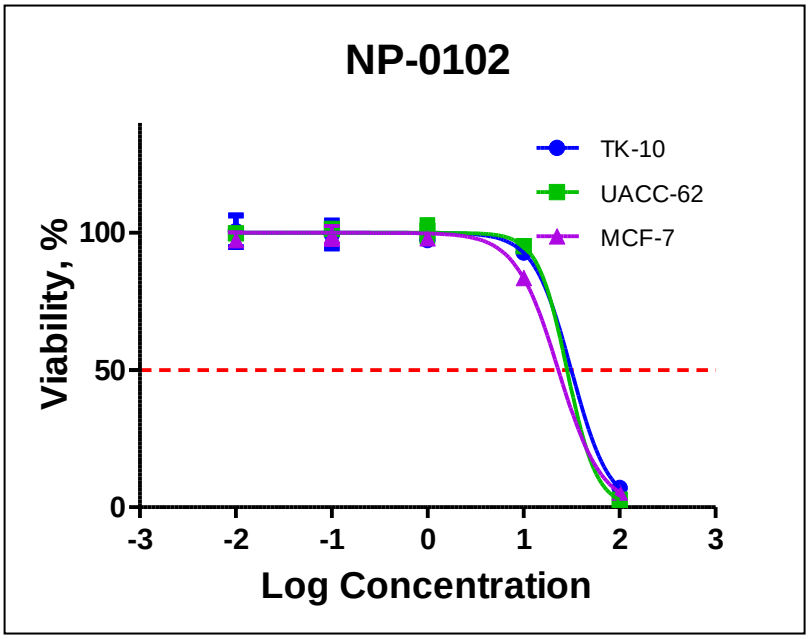
	TK-10	UACC-62	MCF-7
IC50, µg/ml	45.76	26.75	23.75



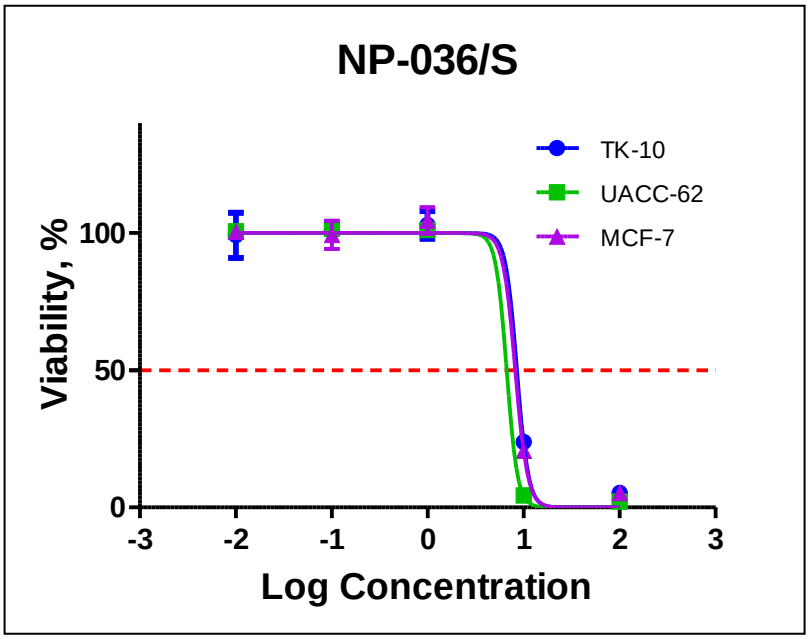
	TK-10	UACC-62	MCF-7
IC50, µg/ml	9.99	7.18	7.41



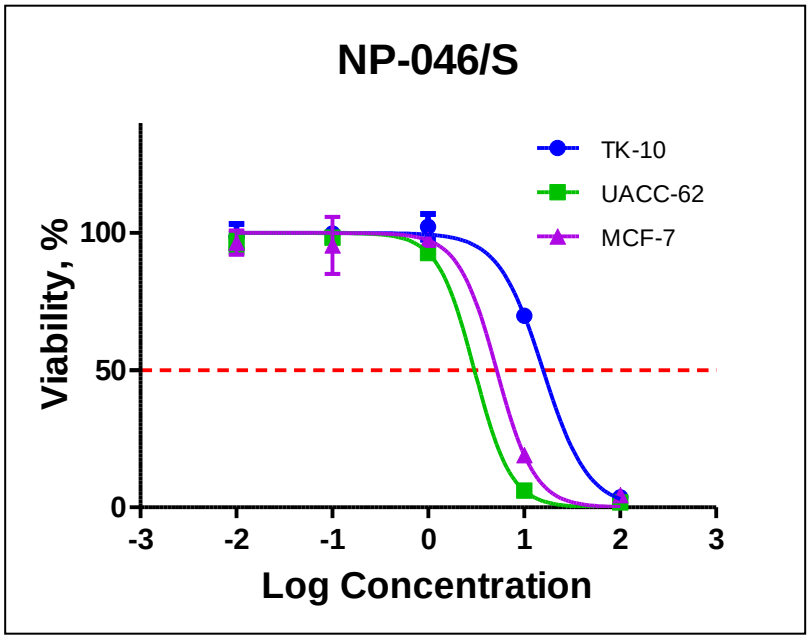
	TK-10	UACC-62	MCF-7
IC50, µg/ml	31.44	28.45	23.11



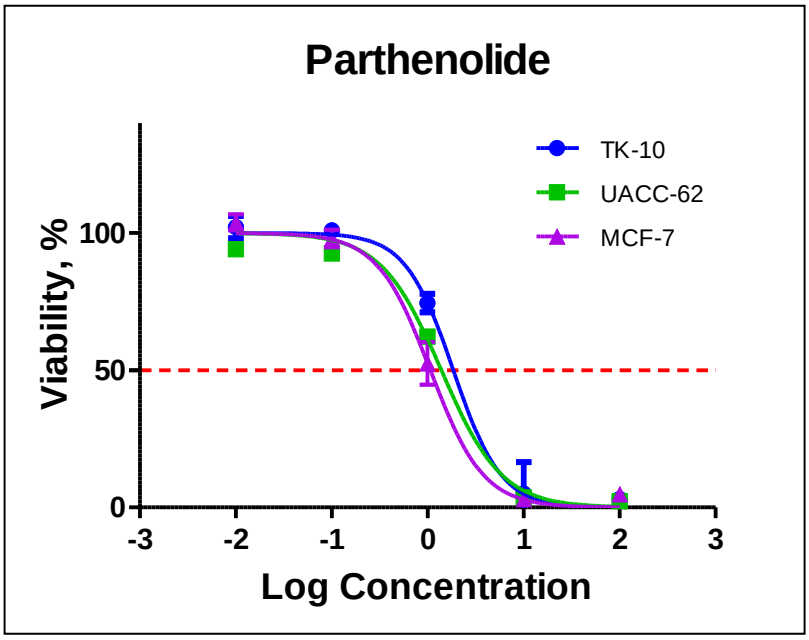
	TK-10	UACC-62	MCF-7
IC50, µg/ml	8.56	6.68	8.22



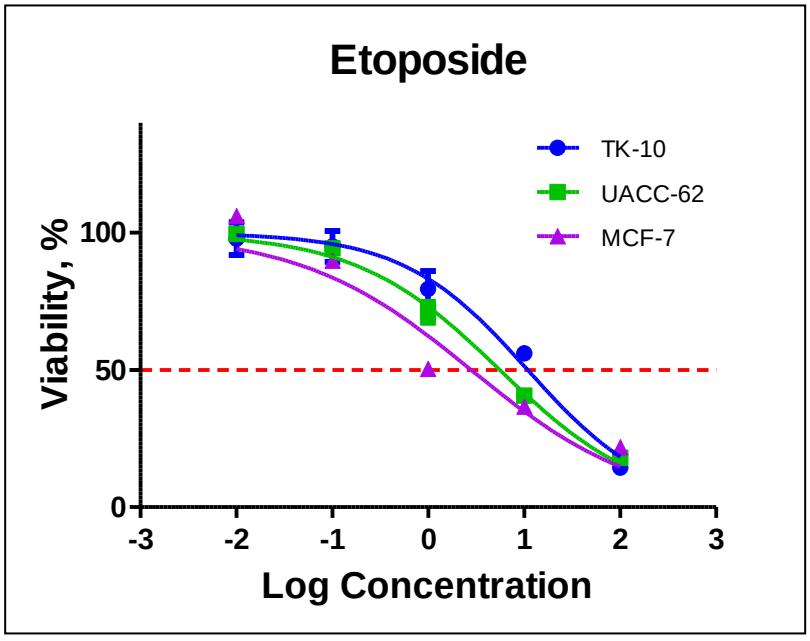
	TK-10	UACC-62	MCF-7
IC50, µg/ml	15.78	3.04	5.17



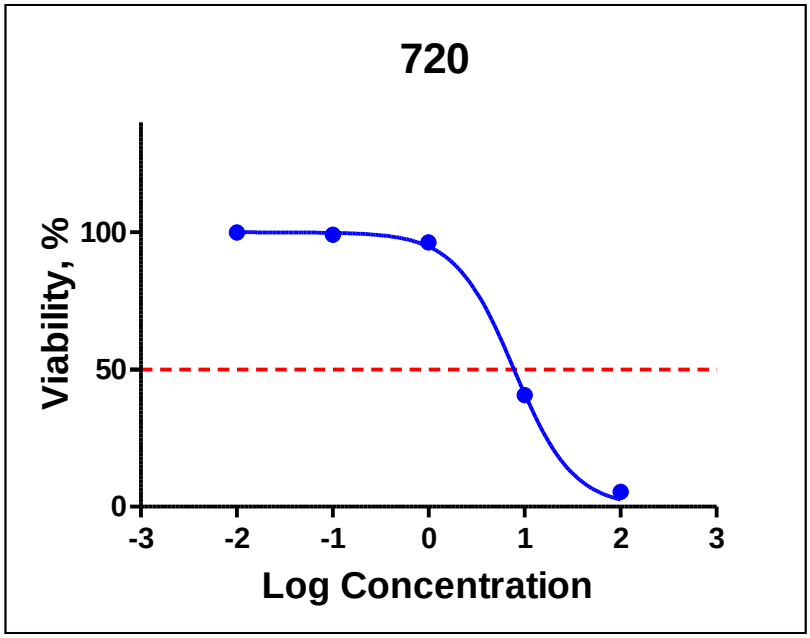
	TK-10	UACC-62	MCF-7
IC50, µg/ml	1.85	1.39	1.07



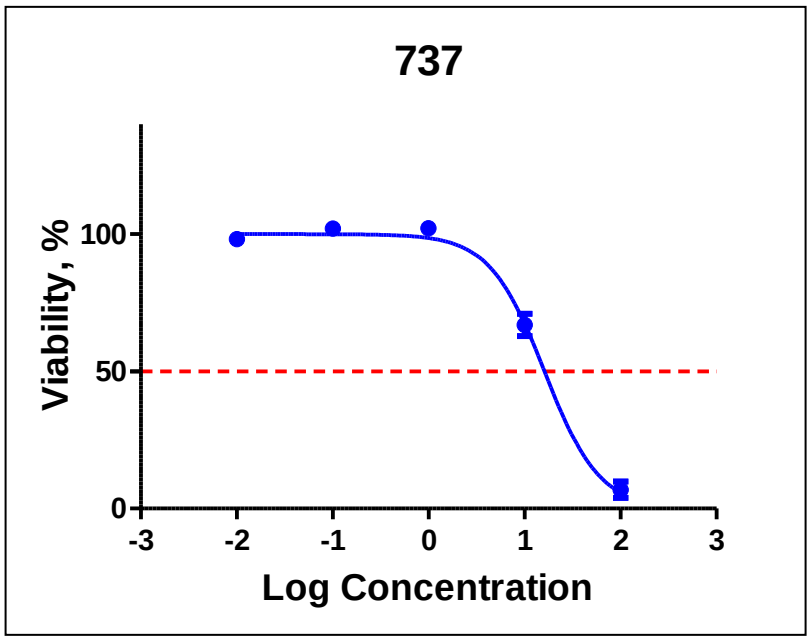
	TK-10	UACC-62	MCF-7
IC50, µM	10.89	5.57	2.81



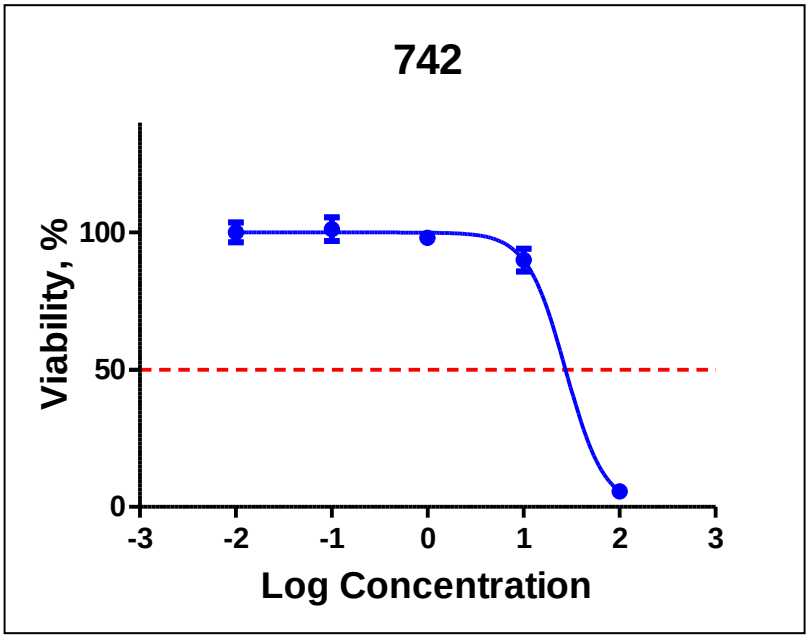
IC50, μM, Hela Cell	7.78



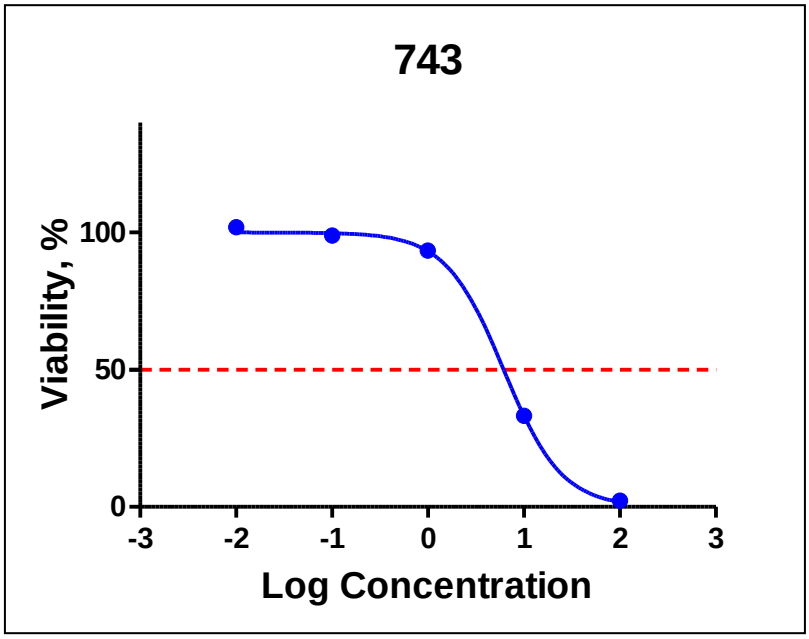
IC50, μM, Hela Cell	16.13



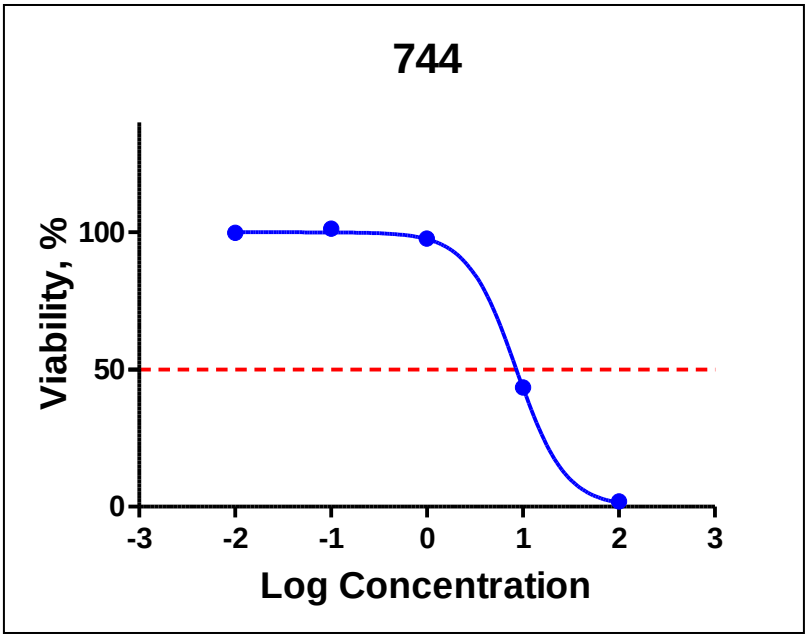
IC50, μM, Hela Cell	27.44



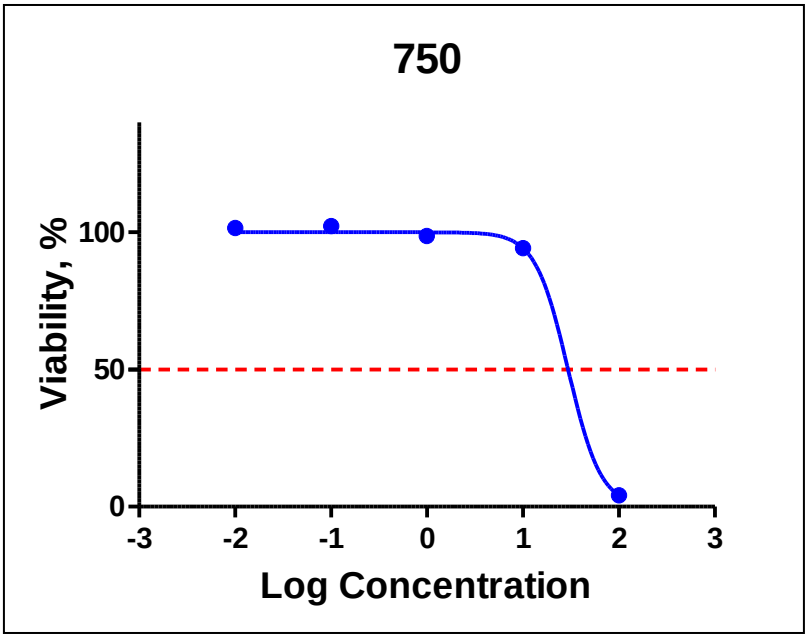
IC50, μM, Hela Cell	6.16



IC50, µM, Hela Cell	8.58



IC50, µM, Hela Cell	29.61



IC50, µM, Hela Cell	0.04